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REPLACES LOST ENERGY

A REVERIE

IN the *Proceedings* of the Section of the History of Medicine, especially in the earlier numbers, there are many references to old MSS., upon which the authors of various papers had to rely to a large extent for their information. In the course of conversation with a former Vice-President of the Section, who desires to remain anonymous, the subject of old manuscripts cropped up, and in this connexion he related to us the following somewhat remarkable experience.

After a busy day he arrived home one evening, and, finding all his family away on some expedition, dined alone in his flat, and after dinner settled himself in an easy chair in his study to browse over some of his favourite literature. The two volumes he had selected to solace his weary brain were an early edition of the Essays from the *Spectator*, and J. W. Dunne's "An Experiment in Time". He dwelt for some time upon The Vision of Mirzah. Readers will remember how Mirzah, lost in meditation on the high hills of Bagdat, was presently taken by the Genius of the huge rock to the highest pinnacle and bidden to cast his eyes downward towards a great tide of water, rising out of a thick mist at one end of the long valley which stretched beneath them, and losing itself in an equally dense mist at the other end. "The valley that thou seest" said the Genius "is the Vale of Misery, and the tide of water is part of the great Tide of Eternity." Across the bridge which stood in the middle portion of the tide Mirzah perceived multitudes of people passing, and realized that these were the generations of mortals in the first stage of their existence. He gazed in wonder upon their various activities as they made their way, slowly and painfully, towards the islands of the blest which lay beyond the mist at the farther end of the valley.

Later on in the evening our colleague picked up Dunne's remarkable book and soon became immersed in its pages. He lingered over the passage in which the author poses the possibility of recalling a fraction of what he assumes to be the lost dreams of some apparently blank nights, believing, as he did, that such fractions should contain images of both past and future events. Those who are familiar with this volume will recall that Dunne urges those of his readers who may be desirous of endeavouring to repeat his own remarkable experiences to make a point of writing down as fully as possible the details of their dreams at the moment of waking, since the impressions received at the time are apt so rapidly to fade and to be forgotten.

Now whether the perusal of these fascinating works had made an unusual impact upon our colleague's tired but excited brain, or whether some mysterious magic had been instilled into the old French liqueur in which, on special occasions, he permitted himself to indulge, we do not know. Suffice it to say that he became more and more drowsy, until at length he fell asleep and, like Bunyan, he dreamed a dream.

He found himself in a small alcove of a magnificent library, sitting at a table on which were piles of old books and documents. Although at first he felt slightly dazed and could not well understand how he had come to be where he was, the surroundings appeared gradually to become more familiar, and he recognized at last that he was in the library of the Royal Society of Medicine, changed indeed, and yet somehow the same as that which he had always known. At first it seemed to him but an hour or so since he had sat in the comfortable arm-chair in his own study, but soon he realized that this was an illusion and that in reality many centuries of earth-time must have elapsed since he had brooded in wonder over the Essays in the *Spectator* and the fascinating speculations of J. W. Dunne. Turning presently to the books and documents upon the table which confronted him, he began to examine them, and soon came upon a curious parchment on which was inscribed a short poem in an ancient language, relating to some matter of historical interest in the affairs of the Society. This he read with avidity. Wishing to know more of its nature and origin, he came out of the alcove, and, walking slowly toward the main door of the great room, he sought the librarian, from whom he hoped to get the desired information. But as he approached the door, the scene began to grow misty and seemed to be dissolving before his eyes. Presently the old familiar objects of his own study began to take shape, and he awoke, and behold it was a dream!

Now what may be the full significance of these events we cannot say. But our friend

was sufficiently impressed by this strange experience to seize his writing materials and to put down at once on paper, as Dunne had urged, the details which had just been presented to him. The words upon the parchment were still fresh in his mind, and with anxious haste he wrote so that nothing should escape him.

The following is the text of the parchment, which we reproduce, without comment on this strange story, for the benefit of such of our readers as may be interested in the fourth dimension and in the history of medicine.

★ ★ ★ ★ ★

FESTA DIES

a.d.sept. Idus Jun. MCMLV.

GAUDEAMUS.

Afflue, Musa, mihi festum sollemne canenti
Quod, decus exaugens meritum, celebravit honorem
Praeclari Socii, laeto qui duxit amatam
Reginam auspicio. Medicorum semper amicum
Participem dapibus nostris quaesivimus Illum.(1)
Talia Dorcastrum nobis alimenta paravit
Qualia Lucanus(8) descripsit carmine docto:—
"Explicuitque suos magno Cleopatra tumultu
Nondum translatos Romana in saecula luxus . . .
Quod pelagus Nilusque dedit, quod luxus inani
Ambitione furens, toto quaesivit in orbe."
Mensis iam positis, magna considit in aula,
Arrectis animis medicorum docta caterva.
Adveniunt proceres; sequitur regalis et Ille(1)
Quem placet insignem sociis captare sodalem.
Corpora sustentant escae; nunc hora bibendi;
Nec procul est geniale merum quo corda levantur.
Mox quoque gaudentes, animos ad sidera tollunt
Cenae participes, et abundat blanda voluptas.
Omnibus expletis cena, vinoque beatis,
Inde, magistratus induta veste, resurgit
Conspicuus Praeses, noster Gulielmus,(2) et Illum(1)
Alloquitur venerandum et clara voce salutat:
'Te comitem accipimus laeti'. Cui rite recepto
Tradidit et signum magnique volumen honoris.
Tum dedit assiduus librum Mauricius(3) auctor
Qui tenet annales et prisci temporis acta;
Illum(1) etiam decuit dextrae conjungere dextram.
Maximus eloquio facundo dixit et Ille(1)
Gratificans; laeto conclamat turba tumultu.
Surrexit Franciscus(4) eques, verbisque peritis
Indigus exquaesivit opes pro bibliotheca.
Suppliciter poscens, itidem mendicat ab omni
Hospite divitias sociis Arturus(5) egenis.
Concilii Magni iam dux dominusque Robertus(6)
Colloquium fecit longum; nec deficit alter;
Doctorum senior, rerum fandique peritus,
Ultimus e sociis dixit clarissimus Edgar.(7)
Inde domum repetit conscendens Ille(1) quadrigam.
Mox abeunt omnes: velat nox umida terras.

1. H.R.H. The Duke of Edinburgh, K.G., K.T.
2. Sir William Gilliatt, K.C.V.O., M.S., F.R.C.S., F.R.C.O.G.
3. Maurice Davidson, M.A., D.M., F.R.C.P.
4. Sir Francis Walshe, O.B.E., M.D., D.Sc., F.R.C.P., F.R.S.
5. Sir Arthur Porritt, K.C.M.G., C.B.E., M.Ch., F.R.C.S.
6. The Most Honourable The Marquis of Salisbury, K.G., Lord President of the Council.
7. The Rt. Hon. The Lord Adrian, O.M., P.R.S., M.A., M.D., F.R.C.P.
8. M. Annaeus Lucanus. (Belli Civilis; Lib. X. 109–10; et 156–7.)

JOINT MEETING No. 5

Section of Psychiatry with Section of the History of Medicine

Chairman—Sir ZACHARY COPE, M.S., M.D., F.R.C.S.
(President of the Section of the History of Medicine)

[*February* 8, 1955]

BRITISH PSYCHIATRY IN THE FIRST HALF OF THE NINETEENTH CENTURY

Philippe Pinel and The English

By AUBREY LEWIS, M.D., F.R.C.P.
The Institute of Psychiatry, Maudsley Hospital, London

PINEL is remembered to-day because he showed that cruelty and neglect play no part—except a shameful one—in the care of the mentally ill. This was indeed his greatest achievement, and it is right that he should be honoured as one of those "sainted pioneers" who relieve the miseries of humanity. But he has other claims to our respect and interest. He was, in his intellectual outlook as well as in his humane impulses, a product of the Age of Enlightenment, a younger brother of the Encyclopædists, and like them he was indebted at some crucial points to English influence and example.

In the second edition of Pinel's "Traité Médico-Philosophique sur l'Aliénation Mentale" [28] there is a passage which I should like to quote:

> "In medicine everybody tends to vaunt the results of his own experience and to quote only the facts which support it. But if experience is to provide an authentic and conclusive basis for any method of treatment, then it must be derived from a large number of patients, on whom observations have been made with extreme care, according to a fixed and regular plan, and repeated for some years on exactly the same lines: favourable and unfavourable results must both be reported equally and the respective numbers of each given. In other words, it must depend on an application of the theory of probability, which has been so happily used in studying other matters of importance to society. If methods of treating disorder are to be solidly based, they must henceforward depend on the results of applying this theory of probability: otherwise medicine cannot take on the character of a true science."

How obvious all that is, and how often the warning has had to be repeated. The history of therapeutic efforts and fashions, controversies, successes and disappointments in psychiatry might have been less jerky if Pinel's principles had been heeded. It is still a valid charge against psychiatry that its most characteristic methods of treatment, the psychological, have not been appraised by the method which Pinel judged essential [28].

> "A continual comparison must be made of the proportion that obtains between recoveries and admissions, at different times in the same place or in different hospitals over the same period of time. If the comparison is to be sound, several requirements must have been satisfied: namely, extreme care in supervising the manner in which registers are kept and tables constructed; regular notes compiled with particular detail on those patients who leave the hospital apparently recovered; and precise figures for the number of recoveries, and relapses, and, of course, failures. The elementary mathematics of probability should be applied to the analysis of these data."

How did Pinel come to attach so much importance to this use of the theory of probability? The reasons, I think, are both particular and general. He had been bred in the tradition of the liberal arts and especially the quadrivium: mathematics and philosophy were his chief sustenance as schoolboy and during the formative years, from 17 to 22, which he spent in the seminary at Lavaur. When he turned from the Church to medicine, mathematics provided him with his daily bread. At Toulouse and later at Montpellier he gave lessons in mathematics: and after he had removed to Paris in 1778 he chose the same means of livelihood. He could have begun to practise, but the intrigues which he noted, with aversion, among the members of his profession in the capital, and his poverty and comparative youth, made him prefer to meet his needs by teaching and medical journalism. It was not until 1785 that he gave up the lessons in mathematics; and from his letters it can be inferred

that he did not regard them, any more than his translations and editorial labours, as hack work. His interest in mathematics was therefore keen, and his knowledge probably commensurate. He consorted at any rate with d'Alembert and other men of distinction in mathematics: he was the friend of Condorcet, whom he helped to hide at Mme Vernet's during the Terror; and the bent of his mind is shown by the title of his Master's thesis: "On the certainty which the study of mathematics instils into the judgment of scientific problems."

When Pinel studied at Montpellier [1] Barthez was teaching there and Boissier de Sauvages had not long retired. Vitalist doctrines were put forward with versatile brilliance and convincing dogmatism, as Pinel tells us in his description of Barthez as a teacher, but he also tells us of his own preference at that time for the mechanistic or mathematical approach to physiology and medicine which derived from such men as Borelli and Baglivi, Hoffman and Jurin. But his preference was discriminating. In his "Nosographie Philosophique" [29] he wrote, apropos of de Sauvages:

> "What gratuitous assertions! One cannot read them without disgust if one's taste has been purified by the study of geometry. . . . Are we not entitled to think that the cultivation of the exact sciences has a happy influence on the study of medicine, leading to a surer tact and discernment in distinguishing true observations from those which are equivocal or obscure. But I must add that the principles of the exact sciences cannot be applied unmodified to the course and treatment of disease. All the efforts of Boerhaave, Pitcairne, Jurin and others during the last century have only made one realize how vain were their claims, apart from some of Borelli's work and the physio-mathematical theories of sight and hearing."

And, appealing to the judgment of mathematicians, he quotes the well-known passage in which d'Alembert had ridiculed the "médecins algébristes" who treated the human body as a very simple machine.

It is evident that Pinel was not in the camp of the followers of Stahl, nor happy among the iatro-physicists: but he betrayed a strong leaning to the latter during his earlier professional years. Between 1787 and 1792 he published a number of papers on the application of mathematics to the mechanism of bony dislocation, and during the same period he prepared his annotated translation of Baglivi's works.

Now although Baglivi had been elected to the Royal Society, I have so far brought no evidence that English influences acted upon Pinel directly. Indirectly English influence was, of course, great. Isaac Newton had given that impetus towards quantitative studies in every branch of knowledge which was powerful in scientific thought during the eighteenth century. The French humanists, in their reaction against Descartes, derived views from Locke and other English and Scottish empiricists which influenced the humanitarian movements of which Pinel's reform was an example. And, as d'Alembert pointed out, it was from such sources that the distrust of systems and facile explanations took its origin [4].

> "The physicist must guard above all against seeking to account for what is outside his grasp. He must distrust this passion for explaining everything which Descartes introduced into physics. . . . Facts, and no verbiage, that is the great rule. . . . But in banishing this mania for explaining everything, we are far from condemning either the spirit of conjecture, which in its cautious discernment often leads to discoveries; or the spirit of analogy, which with wise audacity penetrates what Nature seems to wish to conceal and anticipates facts before perceiving them."

The sense of the first part of this extract was reiterated over and over by Pinel: it is his weakness that he could pay little regard to the spirit of the latter part.

But Pinel had made a more immediate contact with English writings and outlook. While at Montpellier he became friendly with an English doctor studying there, and learnt English from him [23]. Thenceforward he read English medical writings attentively, as his references to British works and journals testify. More significant, he translated Cullen's "Institutions of Medicine", relating them constantly to the teaching of Boerhaave and Sydenham, and translated also a selection of papers from the *Philosophical Transactions of the Royal Society*. The introductions he wrote to the three volumes of this translation for which he was responsible, and the articles he chose to include, are indicative of his mathematical bent.

In the introduction to the volume on Medicine and Surgery [25], which appeared in 1791, he wrote:

> "Medicine and Surgery would have always had the first place among the natural sciences if they had been treated with the same thoroughness as they are in the *Philosophical Transactions*. In the studies reported there, observations are rigorously marshalled. . . . The papers are valuable because the authors have limited themselves to reporting facts and the inferences that can legitimately be drawn from these, without wandering off into vague theories and conjectural systems."

And in the Avertissement prefixed to the volume on Anatomy and Physiology [24] he

deplores how men of inexact mind, who prefer brilliant hypotheses and the sterile verbiage of metaphysics, have held up the progress of physiology: but, he goes on,

> "Certain Memoirs in the *Philosophical Transactions* serve as a remedy for this malady of the mind, which has been the cause of so many errors. I have tried to make these memoirs more widely known, as much for their firm logic and experimental rigour as for the novelty and importance of the facts they report."

Among the articles he selected are several concerned with vital statistics. Thus in the Anatomy volume he publishes a long extract, with tables, bearing on the disproportion between male and female births; and in the Medicine volume he translates a lengthy paper on the same subject taken in conjunction with statistics of death and accidents after confinement, to determine the chances of survival. After another paper of demographic interest, he wrote:

> "I thought I ought to present first this interesting research on population, public health, and the means of determining the growth or decline of nations. The English seem further advanced than any other people in calculations of mortality, which have been made among them with the greatest precision, and from which they have been able to draw very useful conclusions. . . . It is much to be desired that these studies, hitherto so neglected in France, should now be cultivated with zeal."

His zeal, indeed, for making these papers known was so great that he reproduced two of them—Dr. White's "Observations on the Tables of Mortality in York", and Dr. Percival's similar "Observations" in Manchester, published six years earlier—twice over, in separate volumes. Both the papers were evidently translated afresh for the Medicine volume, which appeared a year after the Anatomy and Physiology volume, for there are between the two translations many differences of minor detail. It would seem that Pinel, who was notoriously absent-minded, forgot that he had included these articles in the 1790 volume and in his eagerness to set them before his colleagues put himself to the trouble of turning them into French twice over.

In none of these papers is there any sophisticated mathematical treatment of the data. They carry us back, not to Halley or De Moivre, but to Graunt and Petty, and Gregory King. Pinel makes no reference to his fellow-countryman, Deparcieux, nor in this context to Laplace, d'Alembert, Lagrange, Condorcet, or other illustrious Frenchmen who applied the mathematics of probability to social and scientific problems. Although he selects several statistical articles on the mortality of smallpox and the evidence that inoculation is beneficial, he does not refer to Daniel Bernoulli's famous memoir, nor to the notable contributions to the same subject by Trembley, d'Alembert and Laplace [18, 33]. Evidently mathematical arguments interested him little for their own sake but he responded warmly to the promise that by calculating probabilities and departures from probability the efficacy of treatment for particular diseases might be firmly determined. There are passages in his writings which echo or paraphrase the eloquent and prescient statements in which Condorcet in the "Discours Préliminaire" of his Essai, and Laplace in the Introduction to his "Théorie Analytique des Probabilités", proclaimed the advantages of applying statistics to the social as well as to the physical sciences:

> "The calculation of probabilities can make us estimate the advantages and defects of methods that are employed in the less exact sciences. Thus, to find out the best among various treatments used for a disease, it is sufficient to try each of them on the same number of patients, keeping all the circumstances perfectly identical. The superiority of the most helpful treatment will become more and more manifest as the number of patients increases, and calculations will reveal the corresponding degree of probability that it will be beneficial" [20].
>
> Pinel [28] with an excess of confidence, assures us that "the fundamental principle of the calculation of probability will always be easy and simple to apply: one will only have to make in each hospital, where the criteria of cure and failure have been worked out, a simple enumeration of the cases falling into these two groups. . . . Such an analysis, carried out in relation to treatment at the Salpêtrière, shows how experimental medicine can advance firmly and steadily by means of a statistical study of probabilities; but medicine will forfeit this advantage if regard is paid only to favourable outcomes."

Pinel underrated the difficulties and arrived at some mistaken conclusions from his simple calculation of percentages, but his basic principle was sound. He particularly avoided the mistake of omitting failures and including relapsed patients as though they were new ones admitted during the period reported—a potent source of error even in our own time. He passed on his enlightened views to his pupil and friend, Esquirol [12], who wrote:

> "There are honest and sincere doctors who do not like statistics. Have they sufficiently considered that the sciences of observation cannot advance except by statistics? . . . I like statistics in medicine, because I am convinced of their usefulness;"

and who bore witness to his faith by the figures that he provided annually from Charenton, and the inquiry he made into the supposed increase in the number of insane persons in France [9, 11]. Moreover, many of Pinel's non-medical contemporaries knew of his statistical efforts: thus Cuvier spoke of them appreciatively in his report to the Institute on the progress of the Natural Sciences between 1789 and 1807 [3].

But Pinel's statistical example and precepts bore dubious fruit. Mental hospitals did, it is true, begin to publish annual statistics, but the analysis of the figures showed those errors which he had deplored—prejudice, sophistry, and uncritical claims. The grossest examples of this occurred in the United States where, as Albert Deutsch [5] has described, therapeutic optimism went hand in hand with careless treatment of numerical data during the first half of the nineteenth century. In England Burrows was an example of the same irresponsible pretensions, and it was not until the 'forties that William Farr [13, 14] and then Dr. John Thurnam [32] of the Retreat examined and reprobated the methods of calculating recoveries that had been employed. It would be tempting to digress here in order to examine the contribution of these two men, and particularly of Thurnam, towards putting the published statistics of mental disorder on a good footing. Farr's outspoken and vigorous onslaught was along a wide front, and deserves to be re-read. But limiting myself to what concerns Pinel, I must record that Thurnam, though well acquainted with Esquirol's use of statistics, evidently knew Pinel's work only from the first edition of the Traité [27], in which statistical matters receive but the briefest mention. He consequently makes only slight and inaccurate references to Pinel's efforts in this field, and it must be conceded that he goes far beyond Pinel in the careful analysis of his figures: he had, of course, much ampler data to draw upon, and the guidance of men like Farr and Quetelet. Thurnam's book appeared in 1845; Pliny Earle [6, 7] somewhat later (1875 and 1887) wrote a correspondingly critical examination of mental hospital statistics for American psychiatrists. Thereafter the form of statistical tables improved; no superintendent claimed that 90% of his patients were cured; and the mental hospital figures remained for the most part undistorted—and unquarried. At intervals, however, claims have been put forward for this or that method of treatment, which have betrayed the erroneous habits of mind which Pinel tried to correct. If the rules he laid down had been followed, we should have been in less doubt about the efficacy of some methods of physical treatment introduced more than a century after his time, and we are still woefully troubled because psychotherapeutic methods have not been evaluated in accordance with the requirements he stipulated. It need hardly be said that Pinel with all his fervour in "moral" treatment was cool in appraising remedies [29]:

> "It is true of mania as of many other disorders: if there is an art in administering drugs, there is an even greater art in knowing how to do without them on occasion."

It is hard to say whether Pinel's teaching on the use of statistics affected directly the outlook or practice of his successors, apart from Esquirol. The statistical method was brought to bear on many problems of nosology and pathology, but P. C. A. Louis and others who tilled this field owed nothing directly to Pinel, as far as I know, and the same is very likely true of those in England, like Sir Henry Holland [17], who expected much from medical statistics. Holland, in his "Essay on Medical Evidence," writes about pitfalls in judging the value of treatment and about the need for numerical inquiry in language which reads like a paraphrase of Pinel, but although it is likely enough that Holland, who spent so much time abroad, was acquainted with Pinel and perhaps attended his lectures, he makes no reference to him in this connexion.

Another feature of Pinel's outlook was his insistence on the value of such psychology as was then available. Locke and his follower Condillac, were the two men to whom he most often appealed as sure guides in the study of the insane [26]:

> "Can one describe the symptoms of insanity if one has not analysed with Locke and Condillac the functions of human understanding?" . . . "So I had to retrace my steps and study the writings of our modern psychologists, Locke, Harris, Condillac, Smith, Stewart."

Stewart was, of course, Dugald Stewart; Smith, less obviously, Adam Smith. No doubt at the salon of Madame Helvétius, which Pinel frequented, he heard recollections of Adam Smith who had associated with Helvétius, Turgot and Quesney during the time he lived in Paris as bear leader to the young Duke of Buccleuch; it is evident, moreover, that Pinel was acquainted with the "Theory of Moral Sentiments", and was much taken with the conception of sympathy as the universal source of moral feeling and emotion that is there put forward. His friend, the widow of Condorcet, translated this work, and it is her version, published in 1798, that Pinel cites in the Traité.

What I have said so far suggests, I think, that Pinel received more from England than England from him, and that what he got was sometimes first-hand, but more often at one remove, mediated through Condillac and other *philosophes* and mathematicians of his own country. At all events the stamp of Locke and of the English pioneers of political arithmetic

was on him. He was well versed moreover in the English and Scottish medical writings of his time. This was especially true of the writers on insanity, whom he quotes frequently, and of Cullen, whom he translated.

For Cullen he expressed much admiration, and some sharp criticism, as he did for Boerhaave. For Sydenham his admiration was greater, and his criticism milder. Sigerist [31] has pointed out how closely his views of disease followed those of the great Englishman. It is not usual now to regard Pinel's views on general medicine any more respectfully than one would those of a contemporary psychiatrist. But specialism was not then what it is now, and besides being the most eminent alienist in France, Pinel was also one of the two most eminent physicians and teachers in Paris. In a memoir which appeared in the *Lancet* [19] a few months after his death, his "Nosographie Philosophique" is described as "a work which became a classical one not only in France but almost in all Europe and which caused him to be regarded as one of the most imposing authorities in medicine". That this was not uttered in the spirit of obituary flattery is clear from many other testimonies, during his lifetime and since [15, 22, 30]. The "Nosographie Philosophique" is a remarkable book, whose Introduction shows clearly how Pinel valued observation and distrusted theory, how he ranged with confidence through the whole field of European medicine, and rejected among much eighteenth century lumber the illusory efforts at a Linnæan classification of disease. He harked back constantly to Hippocrates, whose works he had read systematically with his friend Chaptal when they were young men together at Montpellier, and he extolled the exact sciences, particularly geometry, as purifying agents in medical thought. We have moved so far in clinical medicine since Pinel's day that the actual content of his "Nosographie" has little interest—far less than the content of his "Traité de l'Aliénation Mentale", for we have not moved quite so far in psychiatry in the last 150 years. But the "Nosographie" reminds us of his cool and critical intellect, whereas in psychiatry we are more apt to dwell on his warm heart and courageous humanity.

I would add only a few words about the effects of Pinel's Treatise upon English thought and practice. Because the York Retreat was founded in complete ignorance of Pinel's work at the Bicêtre, and exerted such a powerful effect thereafter on public opinion and asylum practice in England, we are prone to think that Pinel's influence upon people in this country was negligible. I doubt if this view can be sustained. As early as 1803 [8] an anonymous writer in the *Edinburgh Review* thought Pinel's work well enough known to need to be decried: and a scurrilous, chauvinistic job the reviewer made of it. Then in 1806 Davis's translation of the Traité was published at Sheffield. After Pinel's death, lengthy accounts of him appeared; a full translation of Pariset's Éloge [22], for example, ran through the *Medical Times* [21], from June to September 1845. More important, English writers on mental illness wrote of him, as they did of Esquirol, with admiration, and there is good reason for believing that the "non-restraint" movement owed something to Englishmen's notion of his benevolent aims. In June 1838 R. Gardiner Hill [16] delivered a lecture on "Total Abolition of Personal Restraint in the Treatment of the Insane". In it he described at length what Pinel did at the Bicêtre, and the horrible conditions that had obtained before. "I turn with pleasure from this picture to the more humane and enlightened system which followed the attempt of the intelligent and immortal Pinel, and in which the Quakers took the lead in this country in their admirable Institution, the Retreat. . . . Still, however, much remains to be done: and it is mainly with the view of stating what may yet be accomplished, and not merely stating, but proving that statement by incontestable examples, that I now address you. I wish to complete that which Pinel began. I assert then in plain and distinct terms, that in a properly constructed building, with a sufficient number of suitable attendants, restraint is never necessary, never justifiable, and always injurious, in all cases of Lunacy whatever." Sentiments expressed less vehemently but to the same effect were stated by Connolly [2]. It was not, I think, Pinel's opinions but his practice, that made these reformers feel that they were travelling on his road. Before him men like Daquin and Chiarugi, and indeed the writers of antiquity, had extolled kindness in dealing with the insane, but it was his signal merit that he demonstrated its efficacy beyond all dispute. Gardiner Hill, likewise, and Connolly, had to demonstrate the truth of what they claimed for treatment without mechanical restraint, and to fight for it.

The man who knew Pinel best called him the La Fontaine of Medicine—"the same nicety of observation, the same quickness in seeing relationships, the same knowledge of the human heart, the same simplicity and good nature, the same disinterestedness [10]". Esquirol went on, after making this affectionate comparison, to call him "one of the luminaries of our time"—an exemplar of that troubled and distinguished age which produced men like Lavoisier and Laplace, Bichat, Fourier and Lamarck. He was also, we may well conclude, an exemplar of the qualities that make up the character of the good psychiatrist—qualities of intellect as much as of character, that are required now just as they were when Pinel entered on his charge at the Bicêtre in 1793.

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James Cowles Prichard, M.D., 1786–1848

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MUCH of medical history, or the greater part of it, has doubtless been written by amateurs in the historical method, by people like myself, practising physicians and surgeons. As a result medical history carries more bias than perhaps other branches of history; distortions occur and eventually pass into the realm of fact. John Haslam for instance, perhaps because he was one of the few British psychiatrists whose works were read by the French, is credited with an early description of G.P.I. and James Cowles Prichard is linked, in many a psychiatrist's mind, with the first description of psychopathy. Alexander Walk has recently shown us how much the history of psychiatry is in need of re-appraisal, and particularly the history of British psychiatry.

Professor Lewis has discussed Pinel. The French are associated with a psychiatric revolution but, whilst not belittling their achievements, I consider that a re-reading of the sources does not justify this widely held contention. The hero-worship of Réne Semelaigne, and the characteristic abasement of some British psychiatrist before foreign opinion have both contributed toward this state of affairs. In many respects Prichard's life and work shed an interesting light on some of the reasons for the comparative obscurity of British Psychiatry in Medical History. Here was a leading British psychiatrist of the early nineteenth century whose xenophilia, in my opinion, has done a grave injustice to his forerunners.

James Cowles Prichard was born at Ross in Herefordshire on February 11, 1786, of an old Quaker family, his great-grandfather, Edward, having been imprisoned on account of his religious beliefs. Prichard's father, Thomas, came to Bristol to join a firm of iron and tin merchants, and in this cosmopolitan city Prichard received his early education, chiefly in his own home. He was taught French by an emigré called De Rosemond, Spanish and Italian by Signor Mordenti, "who called himself a Roman", and Latin and arithmetic by

an Irishman named John Barnes. In his memoir of Prichard, published in a volume with the wonderful nineteenth century title of "The Aborigines' Friend", Dr. Thomas Hodgkin, a close friend, tells how Prichard's father devoted every evening to reading English from a French book, often from Rollin's History. He then required his children to give in French what he had said in English. Familiarity with French, and a taste for history were thus imparted at the same time. A very strong inclination to study soon manifested itself, and Prichard was often forced to leave his books in order to have "needful recreation and exercise; yet when he joined his companions in the playground, he entered into their sports with as much animation as the idlest and gayest". His facility for languages was quite remarkable, and he delighted in accosting seafaring men in Bristol in their own tongue. He is said on one occasion to have spoken to a Greek sailor in Romaic, and the man was so delighted that he caught the boy-linguist in his arms, and kissed him heartily. This interest in foreigners and in language was to remain the dominant theme of his life-work.

He appears to have had an early inclination towards medicine, which his father did not encourage, as he desired his son "should retain the primitive simplicity and orthodoxy of genuine Quakerism" which he feared the study of medicine would contaminate. The boy got his wish, and at 17 attended lectures under a Dr. Pole, in Bristol, shortly moving to Staines, where he lived with Mr. Tothill, the partner of the Dr. Pope who subsequently became a physician to George III. In 1804 he attended St. Thomas's, and then went to Edinburgh, where he took his M.D. in 1808. His thesis, which was much longer and more elaborate and learned than such compositions usually are, showed the direction in which his studies were already tending—it was called "De Generis Humani Varietate". It was eventually to become his 5-volume magnum opus, the Natural History of Man. He then moved to Trinity College, Cambridge, where he resided for a year—probably studying mathematics and theology. Here he made a decisive step, renouncing the Society of Friends, and entering the Church of England. This change enabled him to enter as a student at the University of Oxford, where he first resided at St. John's and afterwards at Trinity College, of which he was a gentleman commoner. He took no degree.

In 1810 he returned to Bristol, set up in practice and married the sister of his old friend Estlin. In 1812 he was appointed physician to St. Peter's—a hospital containing a number of patients suffering from mental and nervous disorders. 1816 saw his election as physician to the Bristol Infirmary and, as we might expect, his work on the wards was, it is said, "marked by the learning, skill and energy which characterized all he did". The patients thought otherwise for a doggerel rhyme by one of them tells how

> "Dr. Prichard do appear
> With his attendance and his care
> He fills his patients full of sorrow
> You must be bled today and cupped tomorrow."

They had some reason to be full of sorrow, for he not only bled and purged them freely, but he was fond of applying blisters, setons and other strong counter-irritants. "One issue" called after him, and the subject of one of his articles consisted of "an incision through the scalp from the vertex to the forehead, three or four inches in length, kept open, firstly by dry lint, and after suppuration was established, by peas".

His professional life was passed largely in Bristol for he moved to London to become a Commissioner in Lunacy only a year or so before his death in 1848. He took an active part in the social and intellectual life of Bristol—was a founder of Bristol College, of the Bristol Literary and Philosophical Society, and President of the Medical Library. To his home, the Red Lodge, came eminent foreigners, and the intelligentsia of Bristol, to drink tea from 8–10 p.m. and to discuss a wide variety of literary, historical and ethnological subjects. His marriage seems to have been a happy one, and he had 10 children; one of them, Augustin Prichard, becoming a distinguished surgeon to the Bristol Infirmary, and the author of two entertaining books of reminiscences, to which I owe a great deal.

His works are concerned with three subjects, Ethnology, Psychiatry and Literature. He is certainly one of the giants of Ethnology, whilst his studies of language are quite remarkable. In fact, his psychiatric writings, though of considerable interest, are dwarfed by his anthropological and philological works. None the less it is with these three books, "A Treatise on Diseases of the Nervous System", published in 1822, "A Treatise on Insanity", published 1835, and the volume on the "Different Forms of Insanity in Relation to Jurisprudence", first published in 1842, that we are concerned here. First, let us state who were his foreign contemporaries between 1810 when he qualified and his death in 1848. In France, they included Pinel, who died in 1826, Georget dying two years later, Esquirol, dying in 1840, Ferrus dying in 1861, and Falret dying in 1870. In Germany, Jacobi (1775–1858), Friedreich (1796–1862), and Griesinger (1817–1868).

Prichard's first book, "A Treatise on Diseases of the Nervous System" is a curious work. Considering Prichard's enormous erudition, the bibliography is patchy, the most frequently

quoted author being Ferriar of Manchester, whilst of the French, Pinel, de Sauvages, Bichat, Martinet and Lorry are the only writers he mentions. The book is largely a collection of cases, with an attempt at a broad classification which owes most to de Sauvages, the French nosographer, and to Pinel. Pinel had thought that the primary seat of disease in cases of insanity was elsewhere than the nervous system, chiefly in the region of the stomach and intestines. Prichard likewise divided his cases into uterine, enteric, hepatic and organic classes. The Frenchman had written that he had "attended at thirty-six dissections in the hospital of Bicêtre, and I can declare that I have never met with any other appearances within the cavity of the cranium than are observable on opening the bodies of persons who have died of *apoplexy*, *epilepsy*, *nervous fevers*, and *convulsions*". "From such data", he adds, "what light can be thrown on the subject of insanity?" Prichard comments on this by saying that this remark in fact throws considerable light on the subject—for he considered that vascular factors were pre-eminent in the pathology of mental and nervous diseases, and that inflammation whether primary or secondary, was responsible for the mental changes. As we have already seen, Prichard was a great advocate of bleeding, and the blood ran freely on his visiting days at the Bristol Infirmary.

Although the book was praised by Esquirol, there is little originality and the works of which it is most reminiscent are those of William Perfect, whom Pinel has so greatly admired. It is as though Prichard was setting down in print his case notes, with some connecting but tentative theoretical links, but showing little evidence of any profundity of thought. This is in no way to derogate Prichard, however, for at this period he was engaged in writing some of his most original and brilliant ethnological and philological works.

The main interest of this book in the development of Prichard's thought is the discussion of Pinel's concept of "Manie Sans Delire" that is, madness without any lesion of the understanding. "The victims of this dreadful malady display a propensity to violent paroxysms of rage, which exerts itself upon every person indiscriminately who happens to come in their way." Prichard goes on to say, "that notwithstanding the testimony of such a writer as M. Pinel, I cannot persuade myself that a human being, in the possession of a clear understanding, having therefore a correct apprehension of social relations, of his own interest, and what he owes to others, should suddenly be transported by a paroxysm of rage, without incitement in what seems to be universally and necessarily connected with the movements of anger. All the atrocious murders committed by lunatics have been perpetrated under some hallucination." Prichard's views were to alter substantially over the next twelve years. His description of Moral Insanity, generally regarded as his most important contribution toward psychiatry, clearly springs from his reassessment of Pinel's work.

In his next book a most remarkable transformation has occurred. It is compact, well documented and the theoretical structure and arguments sound and closely elaborated. French influence is dominant, and we become more familiar with the Maison Royale de Charenton, the Bicêtre and the Salpêtrière than with Bethlem or the Retreat. The dedication is to Esquirol, "the most distinguished writer of his age on the subjects which I have endeavoured to investigate. May I thus be allowed to connect with my work a name which will be handed down to posterity as that of one who, by elucidating the causes of the most severe of temporal calamities, and the means of its alleviation, has deserved the gratitude of mankind". Yet this most distinguished writer, in his 2-volume, 1542-page work on Mental Disorders, published three years after Prichard's work, mentions Prichard only twice, devoting 8 pages to a consideration of moral insanity, which he finally rejects as a separate type of madness, including it under the monomanias.

Prichard divided insanity into four groups, all of which are derived from French psychiatric concepts. Firstly moral insanity, by which he meant "madness, consisting in a morbid perversion of the natural feelings, affections, inclinations, temper, habits, moral dispositions, and natural impulses, without any remarkable disorder or defect of the interest or knowing and reasoning faculties, and particularly without any insane illusion or hallucination". Secondly, "monomania" or partial insanity, what we would now call delusional insanity; then mania, or raving madness; and lastly, incoherence or dementia.

The origin of these concepts is of some interest. Pinel, as I have mentioned, has described cases of "emportement maniaque sans delire", and the case Prichard quotes from him is really an example of a man with an ungovernable temper. Unhappily, Esquirol is then brought in, an accessory to the fact as it were, and quoted on moral alienation, which he considered to be the proper characteristic of mental derangement. "There are none in whom the passions and moral affections are not disordered, perverted or destroyed. I have in this particular met with no exception." Georget too was considered to have described a morbid state of the feelings and active principles of the mind, or of the propensities and habits, as a particular modification of madness. In the early nineteenth century, the term melancholia had fallen out of favour with the French, although John Haslam and other

British psychiatrists had given wonderfully clear clinical accounts of manic-depressive psychosis. Esquirol, therefore, introduced his concepts of monomania and lypemania. These were chronic cerebral affections, unattended by fever, and characterized by a partial lesion of the intelligence, affections or will. The monomaniacs showed illusions, delusions, hallucinations, and vicious associations of ideas. The lypemaniacs are the depressives. Prichard, taking a cue from Pinel, split off the moral insanities from this group. Although monomania and moral insanity were not mutually exclusive, each merging into the other at times, Prichard sturdily insisted that there was a specific group of moral insanities. So much so that Esquirol had reluctantly to agree with him, although reading Prichard's case material to-day, it is difficult to see why he did so, and indeed remarkably difficult to understand Prichard's reasoning for separating off a new nosological entity, for his cases are manic-depressives, obsessives, eccentrics and paranoid patients.

Perhaps the reason lies in the political and religious ideas then so powerfully at work both in France and in England. One of the preoccupations of French alienists at this period was forensic psychiatry, particularly in relation to responsibility and the cause of crime. Raymond de Saussure, in his paper on "The Influence of the Concept of Monomania on French Medico-Legal Psychiatry from 1825–1840", has pointed out that before Esquirol, individuals who had committed crimes or misdemeanours were considered mentally ill only if they were in a state of actual delirium or dementia. With the advent of monomania any criminal act could be looked upon as a mental disorder—as an example of instinctive monomania where the patient is drawn away from his accustomed course to the commission of acts which neither reason nor sentiment determine, which conscience rebukes and which the will has no longer the power to control. The actions are involuntary, instinctive, irresistible. Prichard's own attitude to the criminal had changed quite drastically since 1822—now a criminal could so easily suffer from moral insanity and so be irresponsible. Prichard was a lifelong supporter of the Anti-Slavery Society, and his background of Quakerism, his Quaker friends, the non-restraint movement and the general humanitarianism of the time may well have been powerful factors working toward the evolution of the concept of moral insanities. He had, moreover, like a truly conservative Englishman, gone a step farther than the revolutionary French. Crime, excess, extraordinary behaviour, *must* be associated with mental disorder, they were inconceivable in an orderly well-regulated personal and social life. Whatever the reasons, in his last book "On the Different Forms of Insanity in Relation to Jurisprudence" Prichard goes still farther and subscribes to the idea of an Instinctive Madness. This form of mental disease "is one the admission of which involves peculiar difficulties, and is in opposition not only to common prejudices, but to all opinions *a priori*, that any person would be likely to deduce from the philosophy of the human mind; it is moreover liable to the objection that it apparently interferes in many instances with the proceedings and ends of justice. . . . In this disorder, the will is occasionally under the influence of an impulse, which suddenly drives the person affected to the perpetration of acts of the most revolting kind, to the commission of which he has no motive. The impulse is accompanied by consciousness; but it is in some instances irresistible". Prichard is in debt again to Pinel, whom he regards as the original author of this conception, "a man", Prichard says in a revealing passage "of more than ordinary power of observation", who "had a very wide field of experience, being physician to one of the largest lunatic asylums in the world, during a period when the agitation of mind produced in France by the great revolution (when in fact the whole French nation seemed to be mad) filled the hospitals of that country with inmates scarcely more insane than those who remained at large".

For Prichard, then, crime on the whole had become linked with mental disorder—with the delusional states so well recognized in English law, with moral insanity and with Instinctive Madness.

The last of the diagnostic groupings—the Dementias—he again owes to Pinel. Of these insanities he writes "by some persons it may be thought scarcely correct to term this a form of insanity, as it has generally been considered as a result and sequel of that disease. In some instances, therefore, mental derangement has nearly this character from the commencement, or at least assumes it at a very early period. I am, therefore, justified in stating it, after Pinel, to be a fourth and distinct form of madness".

We have seen how greatly Prichard was influenced by French psychiatry, and how remarkably biased in this direction his three books are. His ethnological and philological works abound in references and are copiously annotated, whereas his psychiatric books are almost entirely French derivatives. British psychiatry of the eighteenth century was far ahead of French or Continental psychiatry, and it remains somewhat puzzling as to why so learned and well-read a man as Prichard should have so neglected his forerunners. The impact of the French Revolution on a Quaker later turned Anglican may partly explain this, together with his early love of French, and the direction which French psychiatry took

during his lifetime. His own influence on psychiatric thought is difficult to assess—on the French it was negligible. In 1843 the M'Naghten Rules were formulated, and the 15 Judges certainly took no account of Prichard's views, perhaps an eminently sound decision, in view of the many untenable propositions put forward by Prichard in support of his concepts. British psychiatry was largely concerned with the more humane treatment of lunatics, and it is interesting that Hack Tuke devotes only 1¾ pages to Prichard in his 548-page volume "Chapters on the History of the Insane in the British Isles".

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Dr. W. A. F. Browne

By JAMES HARPER, M.B.E., M.B., M.R.C.P.Ed., D.P.M.

Crichton Royal, Dumfries

WILLIAM ALEXANDER FRANCIS BROWNE was born in Stirling in 1805. His father, an Army Officer, was drowned in a troop transport while on his way to the Peninsular War later in the same year and Browne was brought up in the home of his maternal grandfather. He was educated at Stirling High School and from there went to Edinburgh to study Medicine, qualifying in 1826.

While a student he came under the influence of George Combe, an Edinburgh lawyer, who has been described as "the chief prophet in this country of the new revelation of Phrenology". He also became a close friend of Combe's brother, Dr. Andrew Combe, who had studied under Spurzheim and who for a time was President of the Phrenological Society. These two men made a deep impression on Browne and his interest in Phrenology directed his attention to Psychiatry. In 1828 he left Edinburgh and spent two years on the Continent, mainly in France though he also visited Belgium and Italy. He studied under Esquirol and always afterwards referred to him with the greatest admiration and respect.

On his return from France he went into general practice but continued to be interested in insanity and in 1834 he was appointed Medical Superintendent of Montrose Asylum. While there he gave a series of lectures to the Managers of the Asylum which were printed in book form in 1837. This book, my copy of which is entitled "Browne on Insanity", but which is better known by a condensation of its main chapter headings as "What Asylums Were, Are and Ought to Be", was to have an important effect on Browne's life.

It has been described as "A fighting book written under the impulse of burning indignation". In his description of what asylums were he quotes extensively from the reports of the Parliamentary committee set up in 1815 to enquire into the condition of asylums in England and he paints a lurid picture of the treatment of the insane in the eighteenth century. Writing of asylums as they existed at his time he is only a little less critical giving perhaps too little credit for what had already been accomplished at, for instance, the Retreat. He acknowledges that many of the worst abuses had been abolished but goes on to say, "Much of the present system may be described by negatives. There is no classification, no employment, no exercise. If you pass through an establishment all may be tranquil, orderly and humane but the inmates are lethargically slumbering in chairs, or endeavouring to devise occupation by tormenting their fellows or circumventing their keepers. Men have been proved to have remained seated in the same spot during the day for a dozen years without an attempt to rouse their muscular or mental energies. This species of negligence is often presented in a more hideous form. Patients who are at first perfectly able to walk are allowed to remain in bed; their limbs waste, contract, are partially ankylosed and they ultimately become unable to rise."

He then deals with asylums as they ought to be, describing in detail his ideal asylum its position, architecture, sanitation, heating and so on. He advocates the abolition of barring grounds and their replacement by gardens and farms to be cultivated by patients. He insists on the importance of occupation and makes the interesting suggestion that potentially

curable patients should be paid for their work but that the money should be held for them until their discharge when it will help them to re-establish themselves in the community.

He stresses the importance of classification and says, "to the curable and convalescent our greatest care ought to be consecrated"; for them "there ought to be as much liberty as is consistent with the safety of the whole community".

He ends his book with a peroration on the ideal asylum of the future as a spacious, airy building surrounded by gardens. Sun and air should enter every room—no shutters or bars should be visible. The house and all around it was to be a hive of industry with no compulsion and no corporal chastisement. The inmates would thus earn peace and sound sleep at night.

Browne was, in his own words, "preaching a crusade". His ideas owed much to Pinel and Esquirol but another important influence in determining his attitude towards insanity was his admiration for the work of the great seventeenth century social reformer, St. Vincent de Paul, and it is significant that his youngest son was christened Vincent de Paul.

The views expressed in "What Asylums Were, Are and Ought to Be" must have been regarded by many of his contemporaries as quite unrealistic but they formed the basis of his life's work as by a most fortunate chance he was almost immediately given the opportunity to put them into effect.

A Dumfriesshire lady, Mrs. Elizabeth Crichton, had decided to use the fortune left by her husband to build and endow a lunatic asylum on the outskirts of Dumfries which she intended should be the most perfect in Europe, and in 1838 the building was approaching completion. Mrs. Crichton started to make enquiries about a suitable Medical Officer and was given a copy of Browne's book which had been published the year before. She was so impressed by it that she immediately offered him the post, he accepted it and the Crichton Royal Institution with Browne as Resident Medical Officer admitted its first patient in June 1839.

Browne remained at the Crichton for eighteen years and we can obtain a clear idea of what he was able to accomplish from his Annual Reports, each about 30 pages. Browne says explicitly, "We conceive that the chief use of such annual summaries is to introduce the public into the interior of an Asylum". He always saw the Asylum as part of the community. He welcomed responsible visitors, both medical and lay, encouraged relatives to visit patients and invited members of the public to attend concerts and plays performed by the patients.

From the beginning patients engaged in social and recreational activities of almost bewildering variety including games, lectures, regular dances and concerts, drives and walks into the surrounding countryside and visits to entertainments in Dumfries.

In 1843 the patients started to produce their own plays and Browne makes it clear that he regarded this as a form of therapy. He writes: "The most novel and interesting attempt to render amusement subservient to the objects of treatment was the introduction of private theatricals as a means of occupation to a certain proportion and enjoyment to above one-half of the inmates. It is believed that this bold step in advance was the first of the kind made in Britain." In the following year appeared *The New Moon*, a monthly periodical written and edited by patients and the first journal to be published in an asylum.

Browne insisted on patients being occupied throughout the day and they had to adhere to a rigid daily time table. In his own words: "Every hour has its appropriate object and occupation and they (the patients) become more the creatures of a system and less the sport of their own distempered inclinations." And again: "Whenever it is possible occupation is prescribed not merely as in itself a means of cure but as preparative to all other attempts to remove mental disease. Labour is not, however, on any occasion carried so far as to induce fatigue—the aim is to benefit the patient, not to perform an appointed service or to save expense."

Browne was more than a good administrator, he was an excellent clinician who realized the importance of systematic observation and detailed clinical records. When he first came to the Crichton he instituted a record of each patient's activities which had to be written daily by the attendant in charge, but by 1845 he had come to the conclusion that this was not sufficient and started keeping his own notes. He writes: "It has been tried first to give a full and detailed account of each case on admission and then to continue the narrative annually or as often as events may render necessary. The history of each individual thus contains the progress towards health or aggravated forms of disease from year to year, the prominent features at particular stages, the effects of treatment, whether these consist of failures or successes (and it) enables the institution of comparison between distant periods and new or modified conditions." Elsewhere he writes of making "a philosophical analysis of the individual mind, of its history, condition and capabilities so that the physician may know and be able to act upon and mould the moral nature of each patient committed to his care".

That he made good use of his clinical notes is shown by his detailed observations on various

types of mental illness, including melancholia, mania, general paresis, epilepsy and alcoholism and drug addiction and by his descriptions of various types of hallucinations, delusions and aphasia. As early as 1842 he started a systematic record of patients' dreams and he also noted the significance of behaviour disorder in children. He writes: "It is highly probable that the passions, peevishness, obduracy, mischievous propensities of infants and children, which are attributed to perversity of disposition, are allied to derangement and that perversity of disposition is in itself a disease. . . . Such morbid tendencies may be cured during and by education or they may be overlaid and concealed by the evolution of intelligence . . . but (they) may likewise be the germ of conditions which constitute the framework of the mind and assume the awful importance of disease only when the test of adversity or age is applied."

Browne was of course a supporter of non-restraint which he had introduced at Montrose in 1834 and was always preoccupied with the correct classification of his patients. He was acutely aware of the importance of the patient's first impression of the hospital and kept new admissions in small groups where they had special attention. He also had separated wards for convalescent patients. To these he gave parole freely and in 1846 he writes: "It is now trite to state that large parties of patients from the Institution form a portion of all public meetings; that they pursue their walks and pleasures in the vicinity, unmolested and unknown; that they are permitted to join the family circle of benevolent individuals; that a few alone and unwatched have been allowed to visit former friends and acquaintances."

In his reports he constantly referred to Moral Treatment. In general he meant by this phrase the total regime obtaining at the Crichton but he included as part of treatment individual psychotherapy. In 1844 he writes: "Much of what is designated moral treatment consists in the conferences and controversies of the officers with the patients in the attempt to disentangle the intricacies and confusions of thought; to substitute precise for vague conceptions, hopes for fears, reason for impulse, to convince of error." And he adds obviously with the wisdom of experience: "He (the therapist) will be exposed to satire, he will find his slightest error, or discrepancy, or ignorance, or forgetfulness seized upon and turned against him; and he may be forced to retire from the struggle discomfited and exhausted."

In 1855 he initiated what he called "an attempt to systematize moral treatment, to apply its principles to the insane in groups". This took the form of lectures and discussions on psychology and mental symptoms. These meetings were perhaps the beginning of group psychotherapy, as Browne stated that as far as he was aware this was the first time such treatment had been attempted in an asylum.

For Browne, in common with other psychiatrists of his generation, the word "moral" as a diagnostic label has a wider connotation than it has to-day. He refers for instance to melancholia as "a disease of moral sentiments", but by 1850 he uses the term "Moral Insanity" in the sense of psychopathy.

Like many other psychiatrists before and since, Browne was concerned with the problem of obtaining suitable nursing staff. In his book "What Asylums Were, Are and Ought to Be" he states that the inadequacies of the attendants were one of the worst features of asylums as they then were and wrote: "Their labours ought not to be limited to the administration of food, attention to cleanliness or the prevention of escape (but that) their work should comprise a moral treatment of the most extended and exquisite form." When he came to the Crichton he laid down a number of rules for the attendants; he supervised their work closely, required them to make daily notes on each patient and insisted that each attendant should not be required to look after more than 12 patients.

In 1854 he took another step forward and one of some historical significance. He instituted a course of 30 lectures on insanity to the nursing staff; the first time I believe that this had ever been done and six years before Florence Nightingale opened her school of nursing at St. Thomas's. Introducing the subject in his Annual Report he writes: "To these persons is in great measure committed the management and moral treatment of the insane: . . . they are literally the companions and ought to be the friends and teachers as well as the nurses and guardians of the patients. Yet for this class there is no normal school, no golden road, no road at all to knowledge."

That he remained concerned about the standard of nursing in asylums is shown by a paper he wrote in 1866 entitled "Sisterhoods in Asylums". In this he referred with approval to the work done by religious orders on the Continent, particularly the Sisters of Charity founded by St. Vincent de Paul and advocated that women should be asked to volunteer for work in asylums as a religious duty whether or not they belonged to an Order. In writing this he was, of course, influenced by Florence Nightingale's views on nursing as a vocation.

Browne refused offers to leave the Crichton and go to either Bethlem or the Royal Edinburgh Mental Hospital, but in 1857 a new Scottish Lunacy Act was passed and he felt his

duty to accept the appointment of Senior Medical Commissioner in Lunacy. While a Commissioner he and his colleague, Dr. Coxe, were, according to a contemporary, "mainly instrumental in formulating the liberal and enlightened policy of the new General Board of Lunacy in Scotland and devoted themselves assiduously and successfully to the establishment of new asylums and the introduction of better methods of treating the insane throughout Scotland".

By this time Browne was recognized as the leading Scottish psychiatrist, he was elected a Fellow of the Royal Society of Edinburgh and was President of the R.M.P.A. in 1866. Yet there is a family tradition that he regretted leaving the Crichton and was never so content as when he was in daily contact with his patients. In 1870 he had to resign his post as Commissioner because of increasing blindness. He retired to Dumfries where he lived until his death in 1885.

A Note on James Parkinson as a Reformer of the Lunacy Acts

By W. H. McMenemey, M.A., D.M., F.R.C.P.

Reform in the treatment of the insane began with the recommendation of Daniel Defoe in 1706. The rival psychiatrists William Battie of St. Luke's and John Monro of Bethlem in Moorfields, who in the third quarter of the eighteenth century opposed each other from across the street, were, by all accounts, careful managers, good doctors and solicitous for the welfare of their patients; while William Perfect was certainly a humane physician: indeed in 1776 he freed a maniac from his chains, many years before Pinel started his campaign. Perhaps in the past we have not credited our early psychiatrists with sufficient humanity, forgetting that restraint was often prescribed in the patient's own interest. Thus Thomas Arnold, who, when he wrote his Observations in 1809, had been practising what has been called the humane method for forty years, reminds us that the employment of chains and fetters was often an economic necessity. He says:

> "Chains should never be used but in the case of poor patients, whose pecuniary circumstances will not admit of such attendance as is necessary to procure safety without them, and to warrant their entire exclusion."

When one studies the progress of psychiatry during the period under review one is struck by the apparent apathy of the Government in regard to legislation, and yet, behind the scenes, there was a good deal of activity. At the beginning of the nineteenth century there existed only the Act of 1744, which permitted two magistrates to apprehend and fetter a lunatic, and the Act of 1774, which allowed of the granting of licences to all who wished to keep madhouses. Five Fellows of the College of Physicians constituted a Board of Commissioners who had powers of inspection but no powers of punishment, so that their reports, which were periodically laid before the College Censors, were virtually useless and generally ignored. Yet public attention was being focused on insanity because of the recurrent illness of the King (1765, 1788, 1801, 1804 and 1810), and because of the attack on the life of the King by Hadfield, an alleged lunatic, in 1800. We should pay tribute to those who encouraged reform of the lunacy laws within parliament. Charles Watkins Williams Wynn (1775–1850), who at the time was M.P. for Montgomery, was responsible for instituting the Select Committee in 1806, which, however, only succeeded in getting passed a permissive Act in 1808 for the establishment of county asylums. George Rose (1744–1818), M.P. for Christchurch, moved the setting up of the Select Committee in 1815, and was largely responsible for its success: when he died his place as the leading reformer was taken by Wynn. Amongst the parliamentary reformers of psychiatric treatment we must include Henry Brougham, that stormy petrel Thomas Wakley, and, of course, Lord Ashley (later Lord Shaftesbury).

I should like to end my remarks by mentioning someone who is not generally regarded as a psychiatrist, but who played a small, but, I believe, important part in encouraging reform. I refer to James Parkinson the apothecary of Hoxton, and it is appropriate to pay this small tribute to him in this Section because it is his bicentenary year. He was a remarkable man, hard-working, modest and with many interests, including the notoriously dangerous one of parliamentary reform. His "Observations on the Act for Regulating Madhouses" was published in the early part of 1811 under curious circumstances. In 1807 he had been asked by the nephew and his wife to examine a widow named Mary Daintree, whose neighbours had complained of her wandering round the street at night calling out to imaginary voices and tying herself up with cords. She blamed herself for her husband's death and it was believed that she was suicidal. Parkinson, who was visiting medical officer to Mrs. Burrows' madhouse in Hoxton, was most careful in his examination, interrogating the neighbours and the patient's son before returning to examine her for a second time. After Mrs. Daintree had been under certification for three months she recognized an acquaintance passing by in the street, and spoke to her through the window. As a result of this casual interview she

was eventually released on petition on the grounds that she was no longer insane. Three years later Parkinson was subpœnaed to attend the Middlesex sessions and he learnt that Mrs. Daintree had brought an action against her nephew and his wife for having caused her to be committed to a madhouse though sane. Parkinson gave evidence for the defence. The dramatic moment in the trial, which lasted for seven hours, arrived when Mrs. Daintree's son denied ever having seen or been questioned by Parkinson, which must have shaken the little doctor very much. Mrs. Daintree won her case and her nephew was sent to the Bridewell in Coldbathfields for six months. *The Times* and other newspapers censured Parkinson, for either he was at fault or there had been a miscarriage of justice. The *Edinburgh Medical and Surgical Journal* logically submitted a third possibility, namely that court procedure in England was defective. At first Parkinson was inclined to ignore these criticisms of his conduct, but eventually wrote his "Observations" at the instigation of the College Visitors. His remarks were, as always, very much to the point. At the time he wrote, a physician, a surgeon, or an apothecary could certify a person as insane. He did not question the ability of a physician to do this, but a surgeon was clearly incompetent to certify a lunatic! With regard to apothecaries, their ability varied considerably: the majority were unquestionably sound and competent, but London was infested with quacks.

He thought a definition of insanity always presented difficulties, for the condition could be simulated so readily by cerebral disease or eccentricities of manner. He referred to cases of aphasia which had resembled insanity. He told of one instance where the policeman was put in the strait jacket in mistake for the patient. Parkinson advances many valuable suggestions in this article. The reception order should, he says, be signed twelve or even twenty-four hours after admission and should be subject to immediate review when the patient's condition changed for the better. He asks that legal protection be afforded not only to the patients but to the keepers, the doctor and the relatives. He thinks that in doubtful cases a physician should be called in to arbitrate, and, if necessary, one of the Commissioners, on payment of a fee. The case of Mary Daintree certainly drew attention to the many injustices which existed and to the futility of the vesting of powers of examination in the College Commissioners without giving them powers of punishment. As a body the Commissioners must have appeared incompetent, because one of the counsels in the trial told the jury "However high their situation these gentlemen should be taught that they are not to wear their honours like useless nodding plumes". Parkinson succeeded in vindicating himself, and although it was many years before all his suggestions were incorporated in law I think his remarks were noted, and were doubtless of service to those who sponsored the Act of 1811, which if it did not cope with the problem of the private madhouses was helpful in tightening up the whole procedure with regard to pauper lunatics, and opened the way to later reforms.

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Dr. Alexander Walk: In Prichard's and Browne's time Pinel was already a classic, and it is therefore of interest to see what they thought of him. Browne said that Pinel's fame "depended on reposing unbounded faith in the law of love and kindness as a means of cure". Elsewhere, however, he recalled that Pinel "biased by the timidity of his coadjutors and the spirit of his age seemed inclined to admit the propriety of trying the 'excitement of terror' as a remedy". Prichard was content to derive his ideas on Pinel's methods at second-hand from Georget, and quotes with approval his use of strait waistcoats, straps and the like. There is a good deal of misunderstanding about Pinel's methods; on the very first page of his "Traité" he explains that the patients who were previously chained were now quietly walking about in strait jackets. It is painful to read, in the same work, the page which begins with sunshine—a patient restored to daylight after years of confinement—and ends with tears—the purposeful infliction of pain on a convalescent girl who refused to work. I feel that this aspect of Pinel's methods should not be denied or overlooked.

The tradition that Prichard's Moral Insanity corresponded to what is now called psychopathy or the psychopathic state is still widespread, but in my view erroneous. Prichard's cases were nearly all manic-depressives or obsessionals, or instances of personality changes of organic origin.

I have the greatest admiration for W. A. F. Browne; if I were to add anything to what Dr. Hyslop has said it would be to point out that, even in the early work which has been quoted, Browne's idealism was combined with many hard-headed, practical suggestions which he was later able to carry out. "He who devotes himself to the care of the insane", he said, "must live among them; he must be their domestic associate . . . engage them in converse and listen to their soliloquies . . . watch, analyse, grapple with insanity, and seek his weapons in the constitution and disposition of each individual."

Section of Neurology

President—Professor F. J. NATTRASS, M.D., F.R.C.P.

[*February* 3, 1955]

Facetectomy in the Treatment of Cervical Rhizalgia

By GEOFFREY KNIGHT, F.R.C.S.

IT would appear that relatively few clinics have as yet adopted Frykholm's method of decompression of the cervical nerve roots within the intervertebral foramina as a measure of treating extremely resistant cases of cervical rhizalgia (Frykholm, 1951). Our own hesitation in embarking on this form of treatment was due to the fear that the operative intervention on the pedicles might well produce a local pain as severe as the disability which it was intended to relieve. Experience, however, has shown that the after-effects of the operation are entirely painless.

Frykholm's operation is soundly designed. In the majority of cases in which cervical rhizalgia occurs without associated compression of the cervical cord it is produced by the pressure of a hard osteophyte situated within the intervertebral foramina which is inaccessible to approach by hemilaminectomy. The neurocentral joint cavities on C.3–7 first described by Luschka (1858) consist of small articulations with synovial linings which are developed between the curved upper and lower surfaces of the postero-lateral aspects of the bodies of these vertebrae. As Bull (1948) has pointed out, these joint capsules are extremely strong, and since they are situated outside and behind the intervertebral discs, they must tend to restrict the degree of lateral herniation of the disc. Hence, although median and lateral protrusions of the disc are well recognized as a cause of compression of the cord, or of the cord and nerve roots, it is extremely doubtful whether disc protrusions alone can ever produce intraforaminal compression of a cervical root, whereas osteophyte formation arising from the neurocentral joints can readily do so.

Narrowing of the cervical intervertebral joint spaces at the levels C.5–6 or C.6–7 is frequently seen in association with symptoms of cervical rhizalgia but narrowing by no means indicates disc protrusion. The narrowing is frequently degenerative in origin. Such degeneration will throw an abnormal strain on the joints of Luschka and the articular joints of the pedicle, thus producing arthritic changes in the joints with effusion, periarticular thickening, osteophyte proliferation, and finally, in certain cases, marked thickening and hyalinization of the outer layers of the dura in the affected root producing root sleeve fibrosis. It is suggested that this latter factor is important in the production of pain. In our opinion, however, friction is the principal cause of pain and simple decompression of the root without diversion of the root sheath is effective in relieving the majority of cases. Decompression of the root by hemifacetectomy provides adequate decompression of the cervical nerve roots directly over the hard osteophyte which is usually coming from the neurocentral joint anteriorly.

Scoville, in 1946, advocated the use of high-speed spherical drills for the intraforaminal exposure of cervical nerve roots. Frykholm, independently, in the same year used a dental burr with a vulcanite cutter to produce a similar result. We have found that the dental burr is rather a slow method and that a rapid exposure can be made using 9 and 11 mm. spherical burrs.

The operative steps have been amply illustrated in Frykholm's monograph (1951). The stages of operation consist first, of cutting well into the upper vertebra to expose the ligamentum flavum and the curved line at the junction of the facets. Further bone is removed with the burr to deepen the cut in the lower vertebra below the junction until this lower

portion of bone becomes thin enough to crack away, exposing the periradicular tissue and margin of the ligamentum flavum over the intervertebral foramen. These tissues are separated from the pedicles and excised. Hæmostasis is secured with diathermy and thus the nerve root is exposed, and usually exhibits well-marked angulation from displacement by the osteophyte. In our experience this decompression alone, if adequately performed, is sufficient to relieve the pain, and we have not found any improvement in the results from the further step of dividing the root sheath and dealing with the arachnoid adhesions internally.

So far, since 1952, our experience of this method has been limited to some 20 cases operated upon at the South-East Metropolitan Regional Neurosurgical Centre on account of intractable pain which had completely failed to respond to all forms of conservative treatment. This number is small but relatively significant bearing in mind the well-known success of conservative measures in the majority of cases of this type. The operation has been restricted to cases of rhizalgia without cord compression, in which myelography has excluded the presence of a disc and in which oblique X-rays have shown the presence of an osteophyte in the intervertebral foramen. The operation has been performed bilaterally and upon multiple roots of the same side with an equal measure of success. The method has relieved not only the sensory symptoms of pain and paræsthesia but has also restored the muscle-wasting seen in certain cases of cervical rhizalgia.

The operation has also produced evidence that certain syndromes that appear to be produced by compression of multiple roots as judged by standard clinical data, are, in fact, produced by a single osteophyte in patients whose cervical nerve roots are arranged otherwise than according to the idealized plan which we have come to accept. Undoubtedly, our views concerning the root distribution to skin dermatomes and muscles are founded on the basis of a clinical average from which there are wide variations.

Sherrington (1899) defined two principal operations in the segmental innervation of the extremities due to pre- and post-fixation of the plexus.

Stookey (1930) claimed that there was no such thing as a normal plexus, which should always be regarded as pre- or post-fixed.

Van Wagenen (1946) stressed that variations of the brachial plexus were numerous, and Sir Russell Brain, in 1948, described three varieties, with pre- or post-fixation moving up or down one segment.

A large number of different dermatome charts have been prepared in the past seventy years but most of those recorded have the defect that they were founded on the examination of a small number of cases. Herringham in 1886 mapped out peripheral distribution by minute dissections of nerve fibres in the brachial plexus. Thorburn (1893) and Kocher (1906) outlined segmental fields on the basis of data from cases of transverse lesions of the cervical cord. Foerster's observations (1933) on the cervical dermatome were each based on one or two cases. These standardized patterns give an entirely erroneous impression of the constancy of limb innervation from individual to individual. It is when we have the opportunity of observing the collected results of clinical observation on the effect of compression of a single nerve root in many different patients that the effect of variation in the segmental pattern of the body from individual to individual becomes apparent.

Observations on the effect of facetectomy can assist in defining the more common variations and the frequency of their occurrence, the most valuable observations being made by determining the sensory changes in the hand, which are always most marked on account of the known sensitivity of the long sensory fibres.

Frykholm's analysis of the sensory changes occurring in patients suffering from single compression of the C.7 nerve roots illustrates clearly the pre- and post-fixation of the plexus. Where the plexus is pre-fixed the C.7 dermatome will innervate the index finger, but where it is post-fixed it will innervate the ulnar border of the hand. Observation on the segmental motor innervation likewise showed agreement in principle but great variation in detail.

Michelsen and Mixter (1944)				Frykholm (1951)		
Weakness, wasting, and twitching observed			Root involved	Paresis and atrophy observed		Root involved
Biceps	Deltoid		C.6	Deltoid	Biceps	C.6 and C.7
Biceps	Deltoid	Triceps	C.7	Triceps and forearm muscles		C.6, C.7, C.8
Triceps and intrinsic muscles of hand			C.8	Intrinsic muscles of hand		chiefly C.7, C.8 but also C.6

Obviously, pre- or post-fixation of the plexus may account for most of these variations but will hardly explain wasting of the intrinsic muscles of the hand of a C.6 root lesion.

From our series[1] 2 cases may be briefly quoted as presenting atypical syndromes simulating multiple root involvement in each of which a single osteophyte has been responsible for the symptomatology and in which both the motor and sensory symptoms have been relieved by operation at a single level. First, that of Mrs. W. in whom X-rays produced evidence of osteophyte formation at C.5–6 interspace which produced compression of the 6th cervical nerve root. Pain radiation and numbness first involved the tips of all the fingers, later the area of sensory disturbance contracted to involve the index finger only, which was completely numb. The muscle weakness was marked and involved the adductor pollicis, triceps, and extensors of the wrist. The triceps-jerk was diminished.

Semmes and Murphy (1943) stressed that the degree of sensory loss in the index finger of patients with compression of C.7 radicular nerve was out of all proportion to that seen elsewhere from compression of a single nerve and claimed that in many persons the C.7 was almost entirely responsible for innervation of the index. There are other examples of sensory post-fixation in our series. Finally, a patient with osteophyte formation at C.5–6 interval on the right side only in whom pain and paræsthesia in C.6 or 7 distribution of the right arm—one cannot say which—was associated with marked wasting of the small muscles of the hand, sparing the thenar eminence. Operation at C.5–6 level has not only led to relief of pain but also to the filling out of the wasted muscles, hence it is unnecessary to suggest the existence of two lesions. Wasting of the small muscles of the hand in association with a C.6 lesion cannot be explained on the basis of pre- or post-fixation, yet it is in keeping with certain of the older anatomical evidence in which it has been stated that the opponens pollicis is innervated from C.6; it is also in keeping with the findings recorded by Frykholm.

In conclusion, I wish to make every acknowledgment to Dr. James Bull and Dr. Frykholm, upon whose original observations this communication is founded.

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Some Disturbances of the Neural Crest Affecting the Nervous System

By J. M. SMALL, F.R.C.S.

INTRODUCTION

From the moment that the primitive streak and the neural groove make their appearance in the few-days-old embryo the possibilities of abnormality arising appear enormous, and in the elaborate differential cell growth that goes into the formation of the nervous system the wonder is that the pattern is so constantly maintained. It is for this reason that it would be wise to anticipate that abnormalities of cellular origin in the nervous system might declare themselves in a similar standardized pattern of varying degree.

Clinical experience has justified such an anticipation, for in the neural crest and closing neural groove we have a cell structure which often undergoes aberration or hesitation in the completion of its task. It is not in the flamboyant examples of spina bifida that I am interested, but in the more elaborate changes which form a pattern repeated under a variety of apparently diverse eventual pathology.

[1] The sensory loss, reflex change and muscle weakness observed in 20 cases was summarized in tabular form. This table is omitted owing to lack of space.

As a clinician my interest in this subject was aroused by similarities in pathology, and although I shall begin with remarks on embryology the eventual picture is one made up of clinical observation and its integration with the accumulated knowledge of embryology.

Embryological Facts

The neural groove and neural crests in the development of the nervous system have been well recognized since the last century, and for over fifty years the contribution of the neural crest cells to the sensory ganglia of the spinal cord has been well recognized. Indeed, the neural crest was named the "ganglion crest" (Fig. 1).

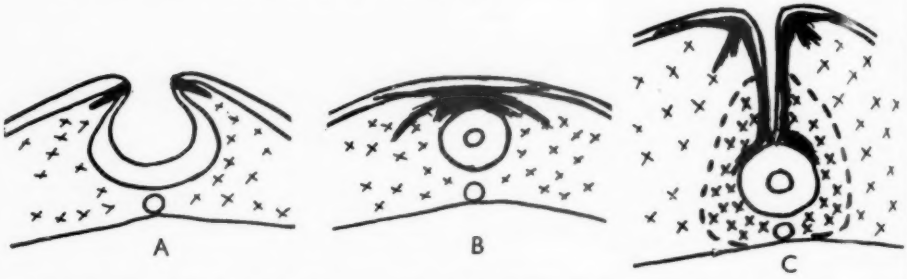

Fig. 1.—The dark shaded area represents the neural crest cells at varying stages of development, and in a case where closure of the neural crest was failing to occur.

A great deal of experimental work has been performed upon the neural crest and its derivatives, particularly just before the war and immediately afterwards. Most of this has been performed on amphibian embryos, but observations on the pig embryo and its similarity to the human embryo in this respect leave little doubt that the pattern of development of the nervous system is essentially a principle in development.

The neural crest may be truly looked upon as a primary organ which only exists in a recognizable state for a short period of time.

The clear definition of the three germinal layers made acceptance of any theory which suggested that apparent mesodermal structure could have an ectodermal origin untenable in many minds, but a vast amount of experimental work, headed by Harrison and Raven, has demonstrated the widespread dissemination throughout the body of cells of neural crest origin.

The experiments devised have been quite fascinating in themselves, and fall into the following main groups: The marking of cells of the neural crest and neural groove by vital stains, or by transplants of neural crests in different species so that the cell nuclei are of different size and therefore recognizable; other methods have been excision of areas of the developing nervous system to see the resulting defects and the transplant of developing neural crest areas into different parts of the same embryo body.

As a result of these experiments it has become clear that the neural crest cells give rise to, or are essential in the development of, the spinal ganglia and sensory ganglia of the cranial nerves, the sympathetic nervous system, the arachnoid and possibly the sheath of Schwann of peripheral nerves. In the cranium they are responsible for branchial cartilages and teeth, whilst the pigment of the retina and the body, including the actual pattern of pigmentation, is of crest origin. The cells of the neural crest appear not only to form certain structures but to act as inducers when related to other cell masses in the production of a systematized structure. This is seen particularly in the neural crest cells relationship with the mesodermal somite of the body. The neural crest cell derivatives seem to have no segment relationship themselves, and are dependent upon the somites for their aggregation into segmental structures. This has been clearly demonstrated by the removal, or addition by graft, of somites in embryos.

Clinical Facts

The first of the clinical facts in the pattern of pathology will be the dermal sinus in the mid-line of the back communicating with structures of the nervous system (Fig. 2).

These sinuses almost always have some angioid pigmentation around them. This naevus, or "port wine stain", is due to hypertrophy of vascular elements in the pigment layer of the skin in which the peripheral nerves terminate. The pattern of these sinuses is constant; the point of termination and the tissues at the termination the only variants (Fig. 3).

It will be seen that the nævus has a relation to the point of primary ectodermal defect and

FIG. 2.—Lumbo-sacral dermal sinus surrounded by nævus.

not to any one dermatome, for these abnormalities may involve several.

Thus a sinus may terminate at the arachnoid, the central canal of the cord, in an elaborate dermoid structure, or an organized central bone peg in the neural arch structure causing splitting of the spinal cord. These abnormalities may occur at any level.

There is, therefore, a systematized pattern leading to dermoid, epidermoid and lipo-angiomatous tumours, and, of course, any of these may occur without leaving a tell-tale mark behind them on the skin surface. It is astonishing in operating on these abnormalities how constantly large and multiple blood vessels are associated with these tracks and lipomata. It would seem, indeed, that vascular abnormalities follow closely in the wake of disturbances in neural crest closure. This is not surprising for the neural crest cells act continually not only as formers but as inducers of structures, particularly in the closely related mesoderm of the somites.

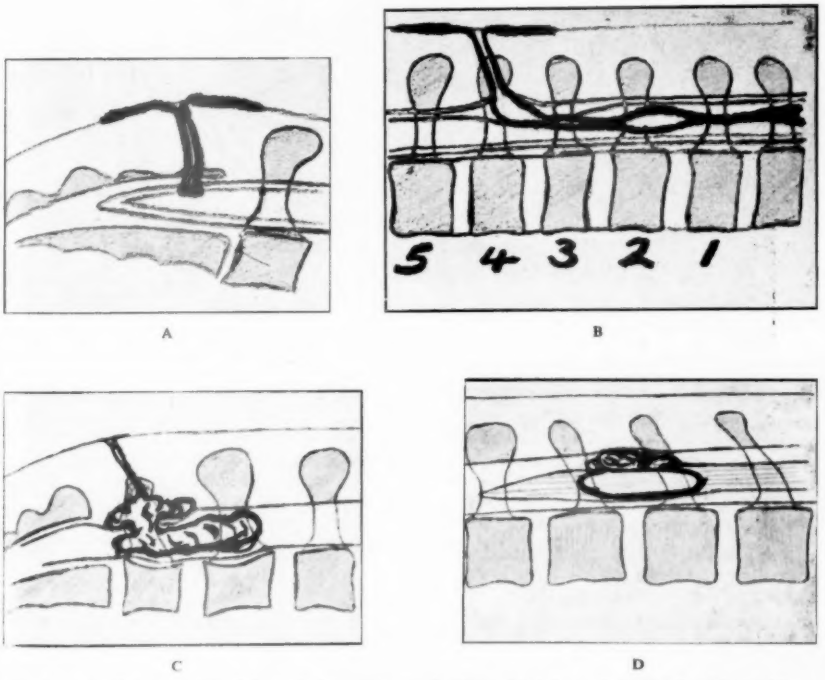

FIG. 3.—Showing varieties of dermal sinus communicating with (A) arachnoid; (B) epidermoids; (C) lipomatous mass; (D) lipoma and intramedullary dermoid without other abnormality.

So far we have dealt with undoubted congenital lesions in local areas, and now we must turn to the question of disturbances of the neural crest as a system. One example (not illustrated) was that of a man with widespread capillary nævus of the skin, an angioma of the retina, pigmentation of the sclera, and a large benign melanoma in the right lateral fissure of his brain, which at the time of operation behaved like a meningioma.

This surely was an example of a system disturbance, no structure existed in this man's disease process which had not a neural crest origin. The neurofibromata and the syndrome of von Recklinghausen in its neural and vascular manifestations is another example.

The surgeon is familiar with the spinal neurofibromata being common in the posterior spinal compartment and arising from the posterior nerve roots. He is also familiar with the fact that intracranial neurofibromata occur only on the true cranial sensory nerves. We have seen that these nerves owe at least part, and probably a major part, of their origin to the neural crest. It is not always, however, that the histology of a tumour, apparently classical in its morphology, agrees with the surgeon's operative diagnosis, and the clear distinction between neurofibroma and meningioma is not always possible. This is particularly true of certain of the meningiomata occurring in the spinal canal, which I have accepted at operation as undoubted neurofibromata when they have no apparent attachment other than by a neurovascular pedicle to a nerve root, stating clearly that a typical neurofibroma was removed without difficulty and yet the histology shows it to be an angioblastic meningioma.

On the other hand, a similar tumour from the surgeon's point of view may well show a fairly typical histological appearance of hæmangioblastoma.

Still other tumours in their histology may show areas of meningioma, lipoma and undoubted hæmangioblastoma structures lying side by side. Here is an example of a patient who had an obvious cord compression syndrome in the upper dorsal region with an angioma over this area in the mid-line of her back (Fig. 4).

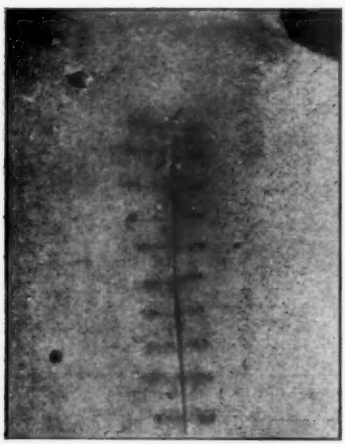

FIG. 4.—Post-operative photograph showing a capillary angioma in the upper region of the incision.

FIG. 5.—X-ray of spine showing angioma of rib.

X-ray of her dorsal spine showed an apparently angiomatous condition of the vertebra spreading into the third rib in the portion which owes its origin in development to the costal element of the vertebra (Fig. 5).

At operation there was a solid tumour in the extradural space intimately connected with the third dorsal root sheath, which was not difficult to remove completely, and histology showed it to be of such mixed variety as I have just described.

Histological sections of the tumour and decalcified bone removed showed the tumour to be of the hæmangioma group consisting of an intricate network of dilated capillary spaces separated by collagenous stroma, some areas of which are lipomatous. Undoubtedly this was a benign tumour, but whether an extradural hæmangioblastoma or an angioblastic meningioma or even a hæmangioma it is not possible to decide.

It is clear that in this case we see the changes in the skin reminiscent of those undoubted disturbances of the neural crest, a disturbance of bone which is derived from the sclerotome so closely associated with the neural crest in this segment, and finally a tumour develops from the tissue in this area of a diverse vascular and meningeal origin.

One other example of tumour histologically similar to the one I have just described occurred intradurally beneath this sunray-like angioma of the skull (Fig. 6).

Although we might extend our thoughts to the varieties of meningiomata and compare those that calcify and ossify with the deposits found in the normal arachnoid it would be merely a deterioration into detail in this thesis of principle, as would be any description of the ganglioneuromas and neuroblastomas which occur within the spinal canal and in the paravertebral region, also the chemoreceptor tumours, all of which are of undoubted crest origin.

We have all seen angiomata of the spinal cord in which there has been a capillary nævus in the skin overlying an angioma in the vertebra, in the extradural space, and in the spinal cord. From what we have seen it is not surprising that this occurs, and the disturbance of the neural crest in a minor form may well determine the angiomata of the cord in their position and extent.

There is no doubt that the angiomata of the brain are essentially extracerebral tumours, and indeed, the surgeon at times has great difficulty in distinguishing between the frank angioma and the most angioblastic form of meningioma.

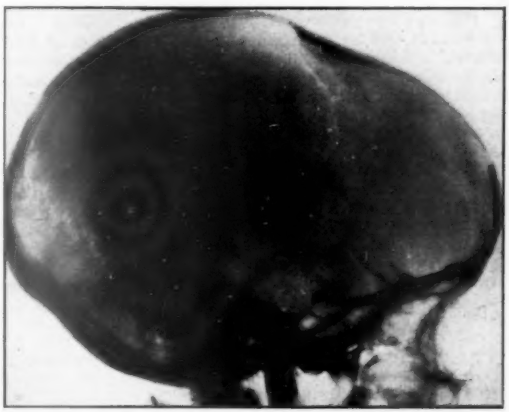

FIG. 6.—Sunray angioma of skull.

CONCLUSION

We have seen a pattern of congenital anomaly repeated in some cases of tumour pathology. The repetition of this pattern, particularly in the spine, is too frequent to be a mere coincidence. The local pattern and the generalized system disturbance seen in the syndromes of von Recklinghausen and Lindau are indeed evidence of system disease. The association of angioma of the cord and hæmangioblastoma of the cerebellum; of angioma and meningioma; of angioma and cystic cavitation of the cord, have all been reported; angioma, pigment disturbance and melanoma of the arachnoid I have demonstrated. The site of these tumours is constant, and probably the reason that congenital anomalies, angiomatous malformation, and certain of the tumours are more common caudally than cranially is because the neural crest of the forming brain closes at an earlier stage than the future spinal cord.

It is interesting that the human embryos with disturbances of neural crest closure which herald either a meningocele or an encephalocele, show not only a non-closure of the crests at the point where the abnormality is occurring, but an exuberant growth of all cell types at this point. So that already there is not only an aberration of hesitation in closure, but of cell growth as well.

It may be suggested that the widespread nature of congenital anomalies and tumours in the varying syndromes is but the result of some disturbances of the developing embryo at a given time. This, indeed, may be true, but if it is, it must be at the time when the neural crest cells are so active in their dissemination through the body that they bear the brunt of this upset.

The search for exactitude in tumour cell origin is perhaps of no great value; indeed, carried to extremes it is a hindrance to clear thought in clinical pathology. This has not been my aim, but I have tried to show a general pattern of pathology which makes the integration of varying anomalies and tumour formations more logical, and therefore more easily understood.

Colloid Cyst of the Third Ventricle

By E. J. RADLEY-SMITH, M.S., F.R.C.S.

IN my experience the usual description of the symptomatology of colloid cysts of the third ventricle does not correspond with the clinical pictures of those I have met.

Loyal Davis says: "Clinically, they are difficult to diagnose, but an intermittent severe headache produced and relieved by sudden movements of the head may suggest the ball-valve action of such a tumour as it obstructs the cerebrospinal fluid pathway."

Bancroft and Pilcher, after briefly discussing their pathology, say: "They are small, mainly because early ventricular blockage and increased pressure are manifestations so intolerable as to spur patients to seek early surgical relief."

I have never had a patient with a colloid cyst who told me of severe intermittent headache dramatically relieved, or produced, by sudden movements of the head. Neither do they appear to seek treatment early, for some of these cysts have been very large at operation.

The first case I have to mention was a man of 41 who had shown a progressive deterioration of behaviour and intellect for the past three years, or perhaps a little longer, as he had not worked for the last three years. Previously he had worked consistently and satisfactorily as a shorthand typist clerk. The only abnormality, before this change took place at the age of 38, was again one of behaviour, for his marriage had been annulled on the grounds of his non-consummation. He had become progressively more untidy, lazy and apathetic and was in an advanced stage of dementia when I first saw him. He was completely disorientated in space and time, having no insight into his condition, doubly incontinent but despite that euphoric to a degree. Neurological signs were very few—perhaps a shade of left facial weakness and a very doubtful left extensor response. In particular, there was no papillœdema. So demented was he, that he could not be expected to complain of headache but his relatives asserted that he had never complained of headache, even before he gave up work three years before.

The provisional diagnosis, not surprisingly, was frontal tumour. Electroencephalography suggested that this tentative diagnosis might be wrong for it revealed no evidence of a frontal focus but indicated the presence of a deep mid-line lesion.

Ventriculography, performed under general anæsthesia on account of his unreliable behaviour, showed that his ventricles were enormous but the fluid not under increased pressure. The enlarged symmetrical lateral ventricles were separated at their anterior ends by a spheroidal mass projecting upwards from the third ventricle—with a rim of air in the very front of that ventricle—and a constriction in the region of the foramina of Monro.

This was clearly a very large ventricular tumour, in no way corresponding to Bancroft's statement that they are small. It was agreed before the operation that the most likely diagnosis by far was a colloid cyst, but, if it were true, it was much bigger than the radiologist had previously seen. On 11.12.50 I removed a large colloid cyst, piecemeal, after approaching it through the right lateral ventricle. After operation he remained uniformly somnolent. His temperature on return to the ward immediately after operation was already 101° F. and he maintained a steady pyrexia between 101° F. and 103° F. for the four days during which he survived. The cyst fluid on analysis showed cholesterol 100 mg.%; the C.S.F. obtained by lumbar puncture post-operatively was opalescent.

The somnolence and the pyrexia, which I believe to be common after piecemeal removal of these cysts, presumably indicated damage to the hypothalamus and it is interesting to remember that he had put on nearly 3 st. in weight in the last two years.

This case therefore presented as a dementia without past history of headache. Members may recall that the late Sir Hugh Cairns also reported a very similar case of dementia due to colloid cyst of the third ventricle.

Another man of 60 years was admitted for investigation of a very similar demented condition. The history indicated the beginning of trouble some three years before but serious symptoms were of only three months' duration. He had become lazy, somnolent, incontinent and even unable or too slothful to feed himself at times. Again there was no papillœdema and the only neurological sign, and that a doubtful one, was equivocal left extensor. The EEG showed generalized abnormality with no focus. Ventriculography revealed large ventricles with normal pressure. Again there was symmetrical dilation of the lateral ventricles and no air could be manipulated into the third ventricle.

This man was deteriorating rapidly and in view of his age and the poor physical and mental condition it was decided not to attempt radical surgery. He died a week or so later and the autopsy showed a considerable hydrocephalus of the lateral ventricles with a colloid cyst blocking the foramina of Monro.

These cysts may, however, show a quite different clinical picture in which dementia is not a feature.

A woman of 29 came to hospital in December 1953 chiefly complaining of failing vision. The first symptom chronologically, however, was "blackouts" which had commenced two years before but had become very frequent in the last two months when she was having 6 a day. In these "blackouts" everything "went dim" for a few seconds. They never occurred except when she was standing. Vision had deteriorated very markedly over the last two months until admission; with her right eye the

could only detect hand movements in the temporal half of the visual field while in the left there was considerable peripheral constriction. Severe bilateral papillœdema was noted. Over a similar period of two months she had complained of severe headaches but they were not sudden in onset or relieved by any change of posture. Apart from the above signs, of general raised pressure, there were no localizing signs: her plantars were both certainly flexor; the cerebrospinal fluid was normal but under high pressure.

Straight X-ray showed a hammer-beaten skull and erosion of the dorsum sellæ. Ventriculography showed huge symmetrical lateral ventricles with no air in the third ventricle. As in the last case the outline of the third ventricular tumour could not be made out. Arteriography showed no lateral shift of the anterior cerebral artery but an undue gap between the anterior and middle cerebral arteries in the lateral view.

At operation a very large colloid cyst was removed from the third ventricle by incising the thin partition between the body of the lateral ventricle and the third ventricle posteriorly from the foramina of Monro.

In this case it was possible to pull out the cyst intact through this incision into the very large lateral ventricle. It was not opened at all while within the skull. This woman is alive and well to-day—some fourteen months later. She escaped the post-operative phase of hyperthermia and excessive somnolence in its severe degree and I am wondering whether the fatal outcome so often encountered may not be partly due to the soiling of the ventricular system with the glue-like contents of the cyst and therefore whether we ought not to take what appears to be the more traumatic course of pulling the cyst out of the third ventricle intact. This woman's cyst was a large one some inch in diameter and had it been removed piecemeal I feel there would have been considerable contamination of the ventricular system.

Two cases have presented in this way with high pressure and symptoms dependent thereon, but without any characteristic type of headache.

In another, a child of 14, the whole history of abnormality was over in twenty-four hours, ending in death before anything could be done. On one day, having previously been apparently quite normal, she reported sick at school with headache, vomiting and drowsiness. On arrival in hospital the next day she was pale, unconscious with irregular breathing and pulse. She had three tonic fits with back arched in opisthotonus, legs rigidly extended, elbow flexed and pupils widely dilated. Her death occurred very shortly after admission without any precise diagnosis having been made. Autopsy revealed a definite degree of dilation of the lateral ventricles with a colloid cyst impacted in the foramina of Monro.

It would appear therefore that these cysts may be a cause of sudden death in people who are believed to be quite fit.

Dr. Russell Barton: The literature concerning the psychiatric effects of lesions of the third ventricle reveals a trend of evidence which suggests that they deserve more than perfunctory dismissal in general terms as dementia or personality change.

Although it is not possible to link a specific mental disturbance to a specific area, manic disorders have been reported in the literature with tumours of the third ventricle and have been provoked by manipulations in the region of the hypothalamus sufficiently often to seem significant. Depressive illness, anxiety disorders, hallucinations, illusions and the peculiar "hypothalamic torpor" are also well reported so that some analysis of the mental state would appear more helpful in approaching the problem of "how" and "where" than the uncritical relegation of mental symptoms to the class "dementia".

There are interesting physiological changes which may accompany hypothalamic disturbance: abnormal bladder activity, thermostatic disturbance, alimentary tract symptoms and hyperglycæmia. I wondered if the last case, of a girl of 14 with vomiting and drowsiness followed by coma, irregular breathing and convulsions, described by Mr. Radley-Smith, had any alteration of blood sugar levels before death.

Mr. Radley-Smith, in reply, said that he had no record of alteration in blood sugar level, but no doubt the opportunity would soon present itself to have this investigation carried out.

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Section of Orthopædics

President—R. WEEDEN BUTLER, M.A., M.D., M.Chir., F.R.C.S.

[*December* 7, 1954]

DISCUSSION ON THE RECONSTRUCTIVE SURGERY OF THE HAND AFTER INJURY

Mr. Ronald Furlong:

A Plan of Treatment for Cut Flexor Tendons

This article deals only with flexor tendons cut accidentally without skin loss.

At first thought it would seem to be desirable to suture a cut tendon as soon as possible. It may not, however, be advisable to do so at the time of primary surgery for the following reasons: Firstly, finger flexor tendons retract and the ends are not available in the accidental wound. The wound is inevitably contaminated and to enlarge it to seek the tendon ends is bad surgical practice, as the contamination is spread. With care and luck and antibiotics no harm usually results but it may; in which case suppuration is more extensive than it otherwise would be. Secondly, enlargement of the wound to expose the tendons may jeopardize the blood supply of the flap so formed. Occasionally, in fact, it is not possible to find the tendon ends by a conventional incision because the direction of the accidental wound will form a skin flap that cannot survive. Lastly, an immediate tendon suture may not be possible because the necessary instruments and skill are not available.

It is useful to divide the course of the finger flexors into three zones.

Zone 1.—This extends from the profundus insertion to the proximal interphalangeal joint. It is a single tendon zone. The disability following division of a flexor profundus tendon is, in this zone, not great; heroic attempts at repair are not worth while.

The tendon is apt to retract through the sublimis bifurcation. Except in instances of obviously heavy contamination the finger should be opened laterally as far as the proximal interphalangeal joint to see if the proximal cut end of the tendon is still visible. If available the tendon is grabbed and an immediate tendon suture is performed. If the profundus has retracted beyond the sublimis bifurcation the surgeon should be content with a skin suture. The wound will have the opportunity of sterilizing itself during the two weeks necessary for sound skin healing. When this is complete the tendon can be approached through the conventional incision and a delayed primary suture is made. If healing is delayed beyond four or five weeks, a later exploration will not be worth while because the bifurcation of the sublimis tendon will be obstructed preventing gliding motion of the sutured profundus. In such a case secondary suture or free tendon grafting are inappropriate. The best result will be obtained by utilizing the distal stump as a tenodesis holding the terminal joint flexed about 20 degrees. If the stump is too short to be used an arthrodesis of the terminal joint is effective but more troublesome to obtain.

Zone 2.—This zone extends from the proximal interphalangeal joint to the proximal end of the fibrous digital sheaths at the level of the distal palmar creases. It is the two-tendon zone. Division of both tendons in this region causes grave disability. Division of one tendon only is usually accompanied by adherence of the other and so the two disablements are similar.

It is fundamental that the sublimis tendon is to be sacrificed when both have been divided or when the sublimis alone has been divided. It is not possible to obtain independent tendon movement if one or both have been damaged in this zone. Removal of the sublimis tendon at the time of primary surgery is not a wise thing to do because of the extensive fishing about that would be necessary. Consequently, primary suture of the profundus tendon is not done for cuts in this zone. The best all-purpose immediate treatment of tendon injuries in this zone is simple skin suture.

A delayed primary suture of the profundus tendon with removal of the sublimis is probably the simplest and best definitive treatment. The opportunity for delayed primary suture expires about a month from the injury. After greater delay, the tendon sheath becomes blocked by proliferated synovial cells effectively preventing gliding motion.

A secondary suture is rarely effective in this zone and anyway a free tendon graft has more to offer. A free graft complete with its gliding mechanism can be adjusted nicely to length and the suture line (a potential point of adherence) is transferred to the palm. The free tendon graft comes into its own as a means of curing the disability of tendons divided in Zone 2.

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Zone 3.—This covers the palmar course of the tendons to the wrist. Flexor tendons may be damaged in the palm as part of an extensive injury involving skin loss and metacarpal fractures. The injury is apt to be extensive indicating that skin healing may be delayed. The tendons do not retract very far and surgical approach to the palmar structures through approved incisions is easy and trouble free.

Incisions accidentally made in the palm may be slow to heal. If tendons, divided in the palm, are not sutured within four to six weeks the proximal ends are liable to become degenerate and friable. This almost completely precludes the possibility of a successful secondary suture. Except in the most unusual circumstances the sublimis tendons should be removed if they are damaged in the palm.

At primary surgery it is more important, in this zone than any other, to secure coaptation of the profundus tendons. The tendons do not degenerate when they are held in tension. Immediate tendon suture maintains the tension even though it may not secure mobility. Fortunately the tendons do not retract very far and enlargement of an accidental cut in the palm is usually easy.

It is worth while, therefore, to enlarge a contaminated wound in the palm so that the profundus tendon ends can be found and sutured. If adherence follows, a tenolysis is more likely to be successful than a secondary suture or even a tendon graft.

Mr. R. G. Pulvertaft:

Treatment of Damaged Skin

It is of supreme importance to obtain skin cover in wounds of the hand and during the primary treatment of open injuries, bone, tendon and nerve repair must take second place to closure of the skin.

I shall discuss the various methods which may be used to convert an open into a closed injury, and here I quote a remark once made to me by Sir Harry Platt, "The man with a method is the most dangerous man in surgery". I have often repeated this to those who work with me, for the sentiment is particularly apt for those who practise hand surgery. Rigid adherence to a favourite method without regard to circumstance can lead one astray. It is necessary to appreciate the results obtainable from different methods and I would suggest that it is our duty to be familiar with the many different techniques available, and to be competent to choose the one most suitable under the existing conditions.

The obvious method of wound closure is, of course, by suture. There is no excess of skin upon the hand, and if suture is to be done successfully without tension, as little skin edge as possible should be removed. It is unnecessary and unwise, in many wounds of the hand,

FIG. 1A.—Original state.

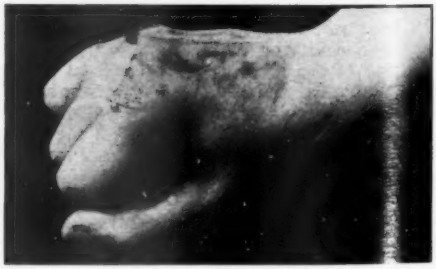

FIG. 1B.—Final state.

FIG. 2A.—Ten days after injury.

FIG. 2B.—After excision of necrotic tissue

to carry out a formal edge excision for in doing so we can create a difficult problem in closure. Careful washing of the wound is usually sufficient provided that there is not severe crushing; if so, excision is inevitable. Fig. 1, A and B, is an example of suture of an extensive laceration—the wound was closed without the use of additional skin, except for that of the filleted little finger, which was damaged beyond redemption.

Skin so damaged that it cannot survive must be completely removed, and here I would draw attention to a form of injury which is sometimes under-estimated. One patient sustained a crush injury with the skin lifted from the thumb, and front and back of the hand, the flaps having distal attachment. Under these circumstances the skin will rarely survive and it is better to carry out an immediate radical skin removal and replacement. In this case, the flaps, after cleansing, were replaced and Fig. 2A was taken ten days later when the patient first came under our care. Fig. 2B shows the flayed and infected hand when the gangrenous skin has been removed. A prolonged and difficult programme of reparative surgery followed, and the result although interesting to us was not what the patient could have expected had his primary care been different.

The replacement of actual skin loss may be achieved by the use of a free graft, or of a skin flap carrying its own blood supply. Free grafts will take readily upon the vascular structures of the hand, but will not survive upon dense cortical bone, joint capsule or tendon; when these structures are exposed some form of flap must be used.

Free grafts may be of partial or whole thickness; the former may vary in depth according to the purpose for which they are required. Thick grafts give the best results in regard to texture, lack of contracture and return of sensation, but they require a good vascular bed, devoid of infection. Thin grafts will survive in the presence of infection.

The local flap of the rotation-advancement type is often of value to overcome small skin defects. It may be used as an immediate measure to cover vulnerable structures upon which a free graft will not survive, or to replace scars which are causing a contracture. The defect should be of triangular shape or brought to this shape by suitable trimming. The blood supply of the flap is safeguarded by careful planning and it is advisable to cut out a pattern in sterile material as a protection against faulty design. Constant observation of the circulation is necessary during the raising of the flap and for this reason a tourniquet is not used. The base of the flap is directed towards the main blood supply and the correct proportion of base to length observed; as a general rule the length should not be more than double the width. The flap should be of a generous size and it is a common mistake to make it too small. The secondary defect is covered by a free graft.

Distant flaps offer the surgeon a wide choice in convenience, quality of skin and size of flap. They may be raised from a neighbouring finger, the palm, the opposite forearm and upper arm, the abdomen and the thorax.

The cross-finger and palmar flaps have a limited use, but at times will provide the solution to a particular problem with the minimum of inconvenience to the patient. Loss of skin on the anterior or antero-lateral aspect of a digit, which is unsuitable for free graft because of the exposure of tendon or bone, may be replaced by a flap raised from the dorsal surface of an adjacent finger. Care is taken to see that the deep structures on the donor finger remain covered by subcutaneous tissue to which is applied a free graft. A flap raised from the palm or thenar eminence can be used to cover a lacerated finger extremity.

Cross-arm and forearm flaps are useful for small or medium size defects which are unsuitable for finger flaps. The skin may be lifted as a single flap or as a bridge leaving double attachment; in the latter case the digit is passed deep to the bridge and thus a more narrow flap may be used without fear for its blood supply.

The abdominal and thoracic flaps (undersurface of the breast in women) offer an almost unlimited supply of skin. They are of particular value when several digits or a large area of hand or forearm need skin covering.

By one or other of these means, or by a combination of them, it is possible to close open wounds of the hand and thus avoid prolonged granulation which leads to stiffened joints, adherent tendons and skin contractures. Far more can be accomplished by reconstructive surgery if the hand is supple and mobile. The final result depends directly on the quality of the primary treatment.

Mr. Donal Brooks:

The Place of Tendon Transplantation in Injuries of the Hand

Injuries to the median and ulnar nerves at the level of the wrist-joint are rarely isolated; some damage to the long flexor tendons, to a greater or lesser extent, is inevitable. The problem of restoration of intrinsic muscle function by tendon transplantation in irreparable nerve lesions is therefore a difficult one. Those motor tendons normally employed in other paralytic disorders are often damaged; scarring may be extensive.

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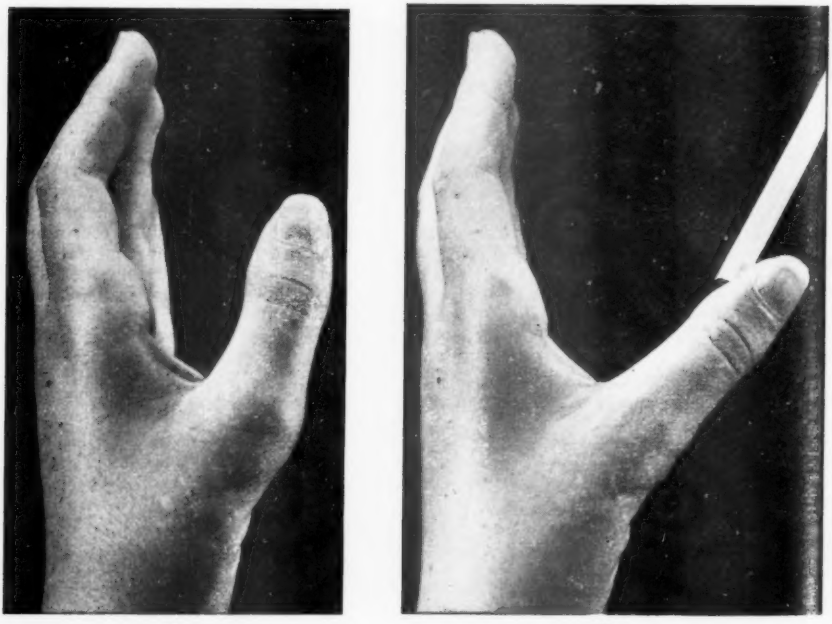
The three significant disabilities resulting from a total paralysis of the intrinsic muscles of the hand are: (1) Loss of opposition of the thumb. (2) Loss of opposition of the fingers. (3) Loss of lateral movement of the fingers, and in particular, loss of radial deviation of the index.

There are two types of reconstructed hand: (1) That equipped for fine work in which a pinch grip between a finger and thumb is essential. (2) That useful for rough work in which a strong grip is necessary.

It is wise to assess at an early stage into which category a given case belongs, having regard to the quality of sensibility that will be present in the hand. For fine work the three important disabilities already mentioned must be corrected—restoration of one function without the other two is not of much value. For rough work, restoration of opposition of the thumb and of intrinsic muscle action in the fingers is not essential.

The principles of tendon transplantation.—(1) Incisions should be so planned that they will skirt all tendon junctions. (2) Where possible, tendons should be inserted directly into bone in order to avoid tendon junctions in the soft tissues. (3) The line of action of the transplant should correspond closely to that of the muscle that is being replaced. (4) The power and excursion of the motor tendon should equal that of the paralysed muscle.



A B

FIG. 1.—Pollex valgus has resulted from an opposition transplant in which the flexor digitorum sublimis tendon was inserted in the first metacarpal and *not* into the proximal phalanx of the thumb.

Operative Technique

Thenar palsy.—An isolated paralysis of the short abductor of the thumb may sometimes give rise to no functional disability, as the combined action of the long abductor and short flexor muscles abduct the thumb and, due to the shape of the carpo-metacarpal joint, rotation of the ray then occurs. If, however, there is a total paralysis of the thenar muscles operative intervention becomes necessary.

A sublimis tendon is the motor tendon of choice, though operative details vary considerably. I prefer a slight modification of C. E. Irwin's technique (1942). In this method a loop is fashioned from the superficial fibres of flexor carpi ulnaris at the level of the pisiform through which a sublimis tendon is passed. The tendon then travels across the thenar eminence, over the metacarpo-phalangeal joint, and traverses a bony tunnel at the base of the proximal phalanx of the thumb, to be secured on the other side to the tendon of insertion of the short abductor muscle. By inserting the tendon into the proximal phalanx of the thumb

the extensor mechanism is left unimpaired, hyperextension and stiffness of the metacarpo-phalangeal joint is avoided and pollex valgus does not develop (Fig. 1).

Often the damage to the hand is such that the superficial flexor tendons are not suitable for transplantation, having been repaired, or even excised at the level of the wrist-joint. In these circumstances extensor carpi ulnaris is used as the motor tendon. It is detached from its insertion, passed over the ulnar border of the wrist, and united to the tendon of the short extensor of the thumb which is re-routed and used as a graft. The line of action of extensor carpi ulnaris is such that no pulley is required at the level of the pisiform. The sole drawback to this method is that the tendon junction lies in the soft tissues. A carefully planned incision minimizes the risk of adhesion formation.

The two techniques described may be regarded as the basic transplants for a complete thenar palsy. In certain circumstances other motor tendons can be employed with diminishing success.

Formerly, in those instances in which tendon transplantation proved impracticable, it was customary to use an opponens bone graft. The results, however, were often disappointing; pollex valgus, due to lack of support of the proximal phalanx, was a common sequel (Fig. 2.)

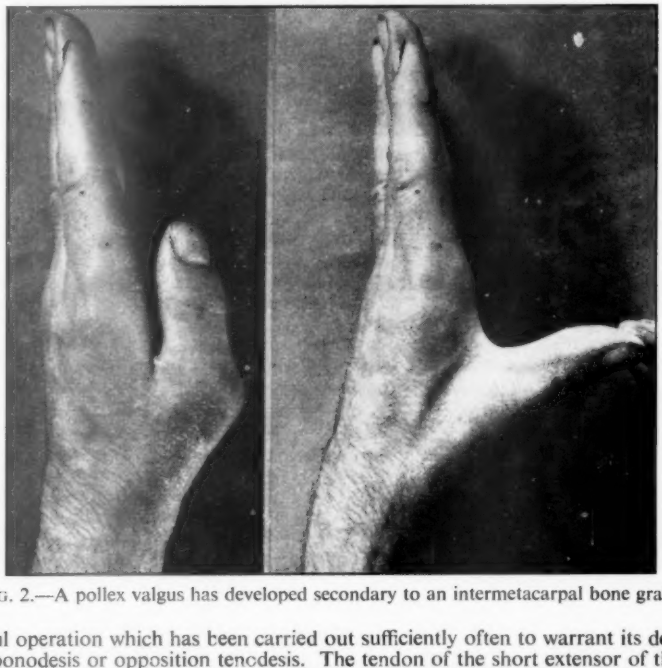


FIG. 2.—A pollex valgus has developed secondary to an intermetacarpal bone graft.

A useful operation which has been carried out sufficiently often to warrant its description is the opponodesis or opposition tenodesis. The tendon of the short extensor of the thumb is re-routed and anchored to the neck of the ulna. The action of the tenodesis is such that when the wrist is palmar-flexed the tendon is relaxed and the thumb can be adducted to the palm, but when the wrist assumes the functional position of slight dorsiflexion then the thumb goes into full opposition (Fig. 3). One of the merits of this operation lies in the fact that as the tendon is secured to the proximal phalanx of the thumb, a pollex valgus cannot develop. Furthermore, the thumb is not held rigidly opposed, as happens after an opponens bonegraft.

Interosseous palsy.—The significant functional disabilities that result from such a paralysis are due to difficulty in extending the fingers when grasping, weakness of grip, and loss of opposition of the fingers. If the deformity is allowed to remain uncorrected then stretching of the extensor apparatus in the fingers may occur. In most cases, if the metacarpo-phalangeal joints are stabilized then full active extension of the fingers is possible. This can be readily demonstrated by wearing a so-called knuckleduster splint.

The classical transplant for this paralysis is that described by Stiles and Forrester-Brown in 1922, and modified by Bunnell in 1944. In our experience the results have not been

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uniformly good. Clawing of the fingers frequently remains uncorrected, and the grip is weaker. One of the causes of failure is adhesion formation at the site of tendon junction.

In a simpler procedure that has given encouraging results the flexor digitorum sublimis tendons are divided through lateral incisions in the fingers and inserted into a tunnel in the proximal phalanx. This gives control of the metacarpo-phalangeal joints without impairing the function of the extensor mechanism or weakening the grip.

FIG. 3.—Functional opposition of thumb on dorsiflexion of the wrist following an opponodesis operation.

First dorsal interosseous palsy.—The first dorsal interosseous muscle has the two important functions to perform of flexion and abduction of the metacarpo-phalangeal joint. Bunnell devised an operation whereby the extensor indicis is transplanted into the tendon of the first dorsal interosseous. The line of action of the transplanted tendon, however, does not approximate to that of the first dorsal interosseous. If extensor pollicis brevis is used as a motor tendon the results are excellent.

In conclusion, the success of tendon transplantation in the reconstructive surgery of the hand depends upon a very careful attention to operative detail—a principle that applies to all hand surgery.

I am indebted to Mr. R. J. Whitley of the Medical Photographic Department of the Institute of Orthopædics, for the photographs.

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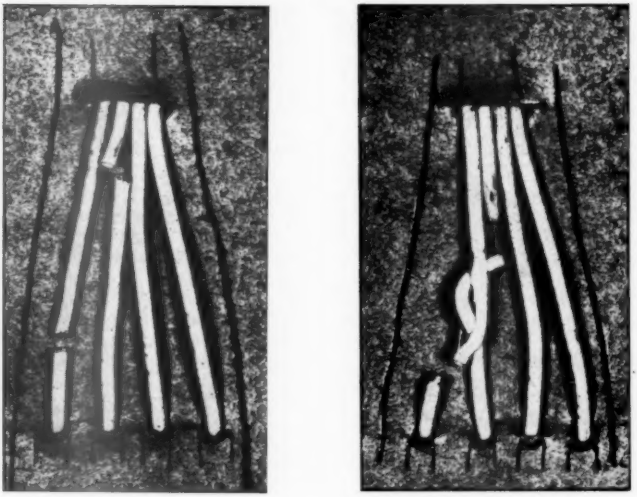
Mr. C. R. Berkin:

Effects of Cortisone on the Healing of Tendons in Rabbits

This paper describes an experiment devised to discover whether cortisone in fairly large doses has a significant effect on the healing of tendons. Carstam of Stockholm (1951) demonstrated that in rabbits large doses of cortisone reduced the amount of adhesion formation around tendons which had been scarified. If it could be demonstrated that cortisone in the doses given did not significantly weaken a tendon suture, then this drug might prove to be of value in human tendon surgery.

In the experiment to be described, 30 rabbits were used. A short pilot experiment was performed in which end-to-end suture of tendons was tried. In all cases at the end of four weeks the suture line was found to have broken down and this method of repair was then abandoned. In the remaining rabbits a modified form of Pulvertaft suture was used. In order to get the required overlap, the tendon of one digit was sutured to the tendon from the neighbouring digit (Fig. 1). The profundus tendon of the first digit was severed distally in the sole of the foot and that of the second digit proximally. The distal end of the second flexor was then threaded twice through and sutured to the proximal end of the tendon to the first digit. The sublimis tendon to the first digit was left intact and the



A B

FIG. 1.—A, Sites of division of profundus tendons to first and second digits. B, Method of suture.

to the second was excised. (These sublimis tendons have been omitted from Fig. 1 for the sake of clarity). The suture material was fine black silk on atraumatic needles. Stainless steel wire could not be used because of the difficulty of subsequent microscopic section. No form of splinting or immobilization was used and the rabbits were free to move about in their cages. The skin wounds healed by first intention in the great majority of control and cortisone animals.

The rabbits were operated on in pairs and the choice of which rabbit should receive cortisone and which should act as control was decided by the toss of a coin. The dose of cortisone given was 5 mg. per rabbit per day in two doses intramuscularly starting the day after operation. Owing to differences in weight between rabbits the dose per kilo of rabbit weight varied from 3 to 6·2 mg., the average being 4·5 mg. per kilo, which corresponds with the dose used by Carstam.

The rabbits were allowed to survive for periods varying from three weeks to four months. Some received cortisone for two weeks and some for three. On killing them the sutured tendons were immediately placed in a machine and ruptured by traction. This machine provides a distracting force with a constant speed of separation. The force in Kg. required to rupture the suture lines was measured on a spring balance. By testing the strength of a suture line immediately after operation the Pulvertaft repair was found to have an inherent strength of 3 kilograms.

Deaths.—No control rabbit died; three rabbits receiving cortisone died, the doses they received all being below the average for the series. Post-mortem examination showed no obvious cause for their death.

Complications.—Sepsis: Infection occurred in three rabbits, one control and two on cortisone. *Hæmatoma:* One rabbit receiving compound F developed a hæmatoma and sepsis in both legs. Both its tendon sutures were found to be ruptured at autopsy, though the skin had healed. These rabbits were discarded from the series.

Of the thirty rabbits, nineteen were allowed to survive for twenty-eight days. These consisted of four groups, as shown in Table I. From this Table it will be seen that the average figure for Group II is lower than that for the control group. However, this difference is less than the standard error of deviation for the groups and is thus not statistically significant. The averages for Groups III and IV are slightly greater than the control group so that it will be seen that cortisone for three weeks does not reduce the strength of tendon sutures in rabbits. Two tendon sutures were found to be ruptured, one in the controls and one in the group receiving cortisone for two weeks. No sutures were found ruptured in the group receiving cortisone for three weeks or in the group receiving compound F. It is felt that these ruptures should be attributed to faults in surgical technique. In all cases the rupture occurred at the suture line. In some rabbits both tendons were tested

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TABLE I.—RABBITS SACRIFICED AT 28 DAYS

Controls		Cortisone for two weeks		Cortisone for three weeks		Compound "F" one dose	
Average:	3·01	Average:	2·39	Average:	3·3	Average:	3·6
Max:	5·3	Max:	4·9	Max:	4·75	Max:	4·75
Min:	1·25	Min:	1·35	Min:	2·25	Min:	2·25
Ruptured:	One	Ruptured:	One	Ruptured:	None	Ruptured:	None
Rabbit No.	Kg. pull to rupture tendon	Rabbit No.	Kg. pull to rupture tendon	Rabbit No.	Kg. pull to rupture tendon	Rabbit No.	Kg. pull to rupture tendon
2	5·3	3	4·9	10	Section	9	Section
	Section		Section		4·75		3·65
8	1·25	24	2·2	18	2·25	13	4·5
	Section		3·5		2·75		Section
12	Section	27	1·35	19	3·6	17	2·25
	4·2		Ruptured		4·0		4·75
15	Ruptured			20	2·75	26	2·5
	3·25				2·75		4·0
16	4·75			21	2·3		
	3·25				3·0		
23	2·5			22	4·5		
	2·6				3·75		
9 tendons		5 tendons		11 tendons		6 tendons	

The figures show the tension in kilograms required to rupture the tendons.

for tensile strength and in others the intact sutured tendon was kept for microscopic section. This accounts for the discrepancy in numbers in the various groups.

Fig. 2 summarizes the experimental results. It will be seen that the strength of the suture line in treated rabbits progresses at the same rate, and in step with that of the control rabbits. Most of these lines are the result of only one or two observations, but those of the groups killed at four weeks are the averages of twenty-five tendon repairs and it will be seen that these two groups correspond almost too nicely for such a small series. Two rabbits killed at four months gave averages of 10·4 and 10·6 Kg. for untreated and treated animals respectively. These figures approach closely to the value of 13 Kg. which was the tension required to rupture a normal tendon.

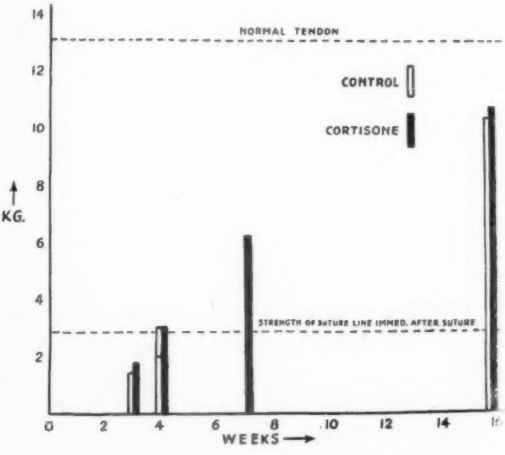

FIG. 2.—Diagram showing the tension, in kilograms, required to rupture tendon sutures in control and cortisone rabbits at various periods from the time of operation.

Histology (Dr. H. A. Sissons).—The points looked for were the quantity and quality of fibrous tissue union, the quantity of necrotic tendon present and the quality of the peritendinous fibrous tissue. There was no apparent difference between the treated and untreated animals in the sections examined. This is in agreement with the findings of Gonzales (1952) and Grant (1953). Buck and Wilhelm (1952) discovered no qualitative difference between control and treated rats, but report a quantitative reduction of fibrous tissue formation in the treated animals. Wrenn *et al.* (1954) report a 40% weakening of tendon repair in cortisone-treated dogs.

Side effects.—(1) Rabbits on cortisone failed to grow hair on the shaved parts until the cortisone was stopped.

(2) Cortisone caused the rabbits' weight to become static, or to decrease. The weight of nearly all the control rabbits increased.

Conclusions.—(1) Cortisone in the doses given, i.e. about 5 mg. per kilo per day does not interfere significantly with tendon union judged histologically or by tests of tensile strength.

(2) It has no effect on skin healing.

(3) Some unknown factor, probably surgical technique, affects the results far more than does cortisone.

(4) Compound F appears to make no difference to the repair of tendon.

As a result of these findings it is felt that a clinical trial of cortisone in tendon surgery is justified. The equivalent dose in a 70 Kg. human would be about 300 mg./day. This dosage was not without its complications in rabbits and might prove too large for humans. A daily dose of 150 mg. of cortisone for three weeks is well tolerated and relatively innocuous provided that the usual precautions are taken.

I should like to thank Mr. J. I. P. James, Dr. A. G. Towers and Dr. J. Tobin for their help and Mr. R. J. Whitley and Mr. Berkshire of the Medical Photographic Department, Institute of Orthopædics, for the illustrations.

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[*February* 1, 1955]

Congenital Dislocation Right Patella, Recurrent Dislocation Left Patella.—W. E. TUCKER, C.V.O., F.R.C.S.

Female, aged 27. First seen on October 17, 1950, at the age of twenty-two years.

Both knees had been unstable since childhood and had felt unsteady. She complained of no pain but the knees tended to swell when they gave way, which happened frequently and prevented her running.

It was obvious that the right patella was permanently dislocated, whereas the left patella could shift in position and tended to dislocate recurrently.

X-rays showed the relative position of the patellæ (Fig. 1).

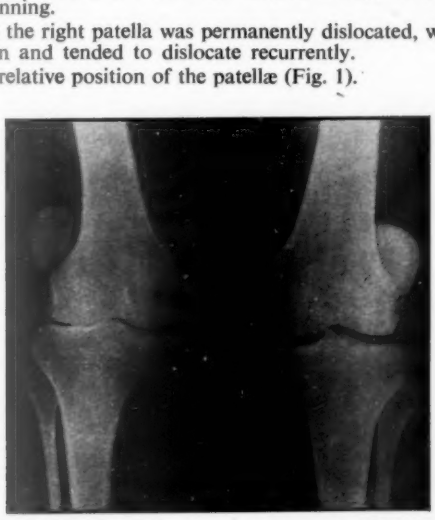

FIG. 1.—Antero-posterior views of the right and the left knee-joints, taken on 20.3.51, showing the right patella dislocated, and the left patella subluxated.

On examination.—Both knees were swollen. There was marked creaking in both, particularly on the right, and there was a considerable amount of synovial thickening. There was marked wasting of both sets of quadriceps, particularly the right.

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On March 20, 1951, the right knee was operated on by combined Hauser and Campbell techniques. It was decided to leave the patella in as removal of it might have materially affected the quadriceps insertion into the patella and the ligamentum patellæ, although it was felt that this might have to be removed at a later date. Recovery was slow, especially flexion, but extension power increased and the quadriceps improved.

On August 8, 1951, a patellectomy was performed on the left patella and the same procedure as before with combined Hauser and Campbell techniques was carried out again. She made a good recovery from this operation and flexion progressed more quickly than in the right knee.

She was referred to the London Hospital for supervision. As flexion of the right knee did not progress satisfactorily, the patella on this side was removed in September, 1953.

Present condition.—She has practically full range of movement of both knees. There is a slight tendency to swelling when she has been on them excessively or exercised them strenuously. There is an occasional ache. Sometimes she has fallen through lack of balance rather than through the knees giving way.

She does not notice any discrepancy in the length of the limbs.

Hallux Valgus Associated with Dorsal Dislocation of the Second Toe.—A. C. BINGOLD, M.B., F.R.C.S.

Case report.—Mrs. D., aged 48, had a painful left hallux valgus and pain under the second left metatarsal head (Fig. 1). Arthrodesis of the first metatarso-phalangeal joint with a compression clamp and excision of the head of the second metatarsal on 8.7.54 followed by a two weeks' course of wax baths and exercises, produced a painless foot. Seven months after the operation she could stand on her feet all day (Fig. 2).

FIG. 1.—Radiograph of patient's left foot before operation.

FIG. 2.—Radiograph of patient's left foot six weeks after the operation showing union of the arthrodesis.

Compression Arthrodesis of the First Metatarso-phalangeal Joint

(1) Pre-operative measurement of the angle of fusion. The patient's heel is placed on a block corresponding to the height of the heel of the shoe she intends to wear. Lines are

FIG. 3.—Method of defining the angle between the first metatarsal and its first phalanx.

drawn over the centre of the first metatarsal and first phalanx and the angle formed by them is measured (Fig. 3). If the angle exceeds 35 degrees arthrodesis should not be attempted. A simple pattern is cut from a piece of sheet rubber which can be boiled and used during the operation.

(2) *Technique.*—A tourniquet is used. Through a medial incision the metatarso-phalangeal joint is opened and the medial sesamoid is excised. The mobilized first phalanx is placed at the correct angle using the rubber pattern, and kept in this position by a holding device, the articular ends are excised and Kirschner wires are then driven through the first metatarsal and its first phalanx and fixed in one clamp (Fig. 4). As the clamp is tightened the bone ends are firmly driven together.

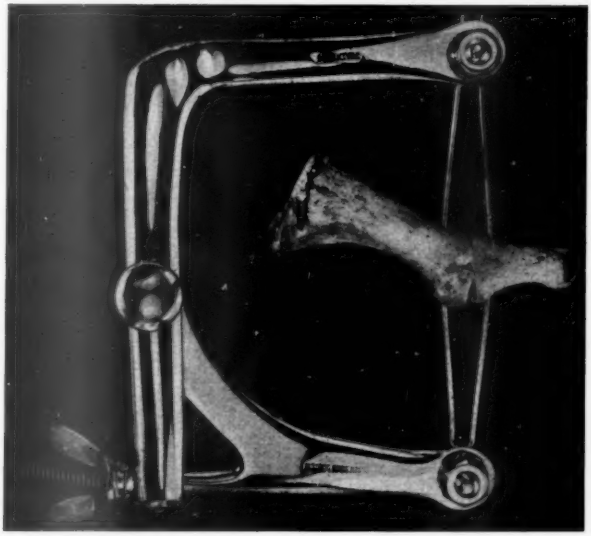

FIG. 4.—Photograph of compression clamp. As the jaws are separated the bone ends are forced together.

After-treatment.—The foot is protected with ample padding and the clamp is plastered on to it. After three weeks the clamp and the wires are removed and a plaster slipper immobilizing the great toe is applied. This is retained for another three weeks. The arthrodesis should be solid six weeks after the operation. Weight-bearing is now permitted and physiotherapy is started but the foot should be supported by longitudinal and transverse arch supports for a few months.

The maximum thrust forcing the bone ends together was found experimentally to be in the neighbourhood of 80 lb. which corresponds to a pressure of the order of 200 lb. per sq. in.

? Osteoid Osteoma Neck of Left Femur.—R. H. V. HAFNER, F.R.C.S.

Miss M., aged 24. Secretary.

History.—Patient experienced pain in the adductor region of her left hip when skating in December 1953. No very definite history of injury. The pain persisted and her own doctor referred her to the hospital. X-ray of the left hip was reported on as showing no bony abnormality. She was given physiotherapy but did not improve and was referred to

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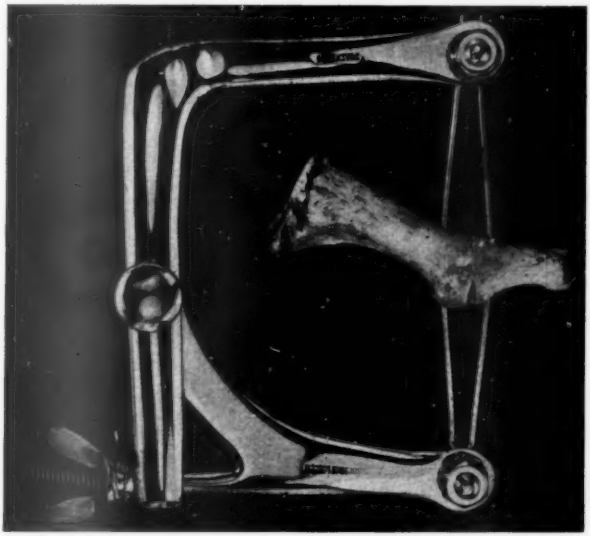

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my Orthopædic Out-Patients Clinic. On clinical examination in July 1954, she had a few degrees of limitation of extension of the left hip but no other abnormality. X-ray showed a buttress of new bone on the medial aspect of the neck of the femur, and she was admitted for further investigation.

Examination under anæsthesia.—There was found to be 15–20 degrees fixed flexion deformity of the left hip and very slight restriction of all movements compared with the right side. No soft tissue or bony swelling was palpable.

Investigations.—E.S.R. 15 mm. in the first hour (Wintrobe).

Blood count: Hb 86% (12·9 grams%). P.C.V. 36%. W.B.C. 8,000; neutros, 49%, eosinos. 2%, lymphos. 47%, monos. 2%. W.R. and Kahn negative.

FIG. 1.

FIG. 2.

Further X-rays were taken: Fig. 1, A.P. view of left hip; Fig. 2, lateral view of left hip. They show new bone formation in relation to the medial aspect of the neck of the femur running from just below the lesser trochanter to the under surface of the head of the femur. Tomograms were taken but did not help in the diagnosis.

Differential diagnosis: (1) *Trauma* (*a*) Partial avulsion of the ilio-psoas tendon with ossification of the consequent subperiosteal hæmatoma. (*b*) Stress fracture of the neck of the femur with callus formation.

This diagnosis was considered unlikely in view of the absence of a definite history of injury and the fact that, in spite of the frequency of injuries in that region, similar appearances have never been seen in my experience.

(2) *Osteogenic sarcoma:* This was excluded when repeated X-ray examination failed to show any change.

(3) *Osteoid osteoma.*—This was considered the most likely diagnosis in spite of the fact that the tomograms disappointingly failed to reveal a definite nidus. There were many features in common with the osteoid osteoma of the neck of the femur described by Sherman (1947); this also was associated with arthritic symptoms in the neighbouring hip-joint.

Treatment.—The hip continues to be painful. The failure to localize the lesion radiologically makes surgical excision difficult. The nidus is usually 1 cm. or less in diameter and in order to be sure of removing the tumour it would be necessary to excise a block of

bone, which might result in a fracture of the neck of the femur. This danger could be overcome by the preliminary insertion of a Smith-Petersen nail or even a nail-plate.

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Comment.—No final diagnosis was arrived at in the subsequent discussion. It was agreed, however, that a biopsy should be carried out.

Rapidly Progressive Destructive Lesion of the Third and Fourth Cervical Vertebræ.—R. H. V. HAFNER, F.R.C.S.

Mrs. G., housewife, aged 51.

History.—In April 1954 onset of pain in the left side of the neck, patient thought this was probably "fibrositis". An X-ray of the neck taken 29.4.54 (Fig. 1) was within normal limits but very careful examination showed loss of clear outline of the superior and inferior surfaces of the body of the fourth cervical vertebra.

FIG. 1.

FIG. 2.

In the beginning of June 1954 the pain began to radiate down both upper limbs. The patient's own doctor referred her to the Physical Medicine Dept. for advice. Further X-rays (Fig. 2) (22.6.54) seven weeks after the first X-rays showed total destruction and disappearance of the body of the fourth cervical vertebra.

On examination.—The patient looked ill and anxious: she held her neck quite rigid. There was a marked flexion deformity and a sharp kyphosis at the level of C.4, there was, however, no evidence of cord involvement.

She was admitted to the ward and immobilized on a plaster bed. The X-rays suggested the presence of a retropharyngeal abscess at the level of the kyphos. An attempt was made to do a laryngoscopic examination but this was unsuccessful and for obvious reasons was not persisted in. General examination revealed no other lesion and rectal and vaginal examinations were normal. X-ray of the rest of her spine was normal, as was X-ray of her chest.

Investigations.—E.S.R. 34 mm. in the first hour (Wintrobe). W.B.C. 9,000: neutros. 70%, lymphos. 30%. Hæmoglobin 100% (15·0 grams%). Urine examination: Reaction acid. Sugar nil. Protein 60 mg.%. Deposit: very scanty pus cells and a few red blood cells. Gram film: Gram-positive cocci plus.

Culture: No growth. No acid-fast bacilli. Bence-Jones protein nil. No bilirubin or urobilinogen detected. Plasma inorganic phosphorus 2·5 mg./100 ml. Serum calcium 9 mg./100 ml. Serum phosphatases: alkaline group 11·2 K.A. units; acid group 4·6 K.A. units.

W.R. and Kahn negative.

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Course.—In view of the very rapid bone destruction it was considered that the diagnosis was more likely a secondary deposit than an infective lesion, in spite of the absence of a primary tumour. However, the patient was started on a course of streptomycin 25.6.54 and isoniazid.

The destructive process spread initially and involved the body of C.3 but this was followed by consolidation. When it appeared that the bone lesion was quiescent the patient was allowed up wearing a plaster collar. She complained of vertigo, due presumably to vestibular nerve damage from the streptomycin.

She was discharged to out-patient treatment 7.11.54, and as serial X-rays showed no reactivation of the condition she was allowed to discard her collar in December 1954 and encouraged to regain neck movement.

Present state.—The patient is up and about and has no pain in the neck or arms. There is no evidence of cord involvement. She has a useful and increasing range of movement of the cervical spine. The latest X-ray (Fig. 3), shows that consolidation has progressed and fusion of the third and fourth cervical vertebræ has taken place. There is no sign of activity.

FIG. 3.

The President said that he had had an almost identical case in 1954 in a man who had started with "fibrositis". He had a very marked muscular spasm of the neck, and was in hospital for three or four weeks during which time numerous investigations revealed nothing abnormal. Eight weeks later he returned with more pain than ever. The X-ray appearances then were almost identical with those shown in Mr. Hafner's case, and were considered probably neoplastic although no primary could be found. Before putting the man on X-ray therapy it was thought justifiable to do a biopsy. Some soft tissue was curetted out from the muscles and on microscopy showed granulation tissue and a pure culture of *Staphylococcus aureus* was grown. The man was put on penicillin and recovery took place within two months.

Arthroplasty of Knee.—J. H. MAYER, T.D., M.B., F.R.C.S.

Mrs. E. H., aged 65.

Rheumatoid arthritis dating from 1950, affecting right hip, both knees, both wrists and both hands. Severe pain continued in right hip and left knee, and by early 1954 she was severely crippled by pain and stiffness in these joints.

June 9, 1954: Modified Judet arthroplasty of right hip, with complete capsulectomy, using stainless steel prosthesis.

Five weeks later she started to stand, the knees having improved during the post-operative period in bed. Pain in the left knee, however, recurred immediately and she found it impossible to take weight on this limb.

August 7, 1954: Arthroplasty left knee using a newly devised technique in which a stainless steel prosthesis fixed to the reshaped lower end of the femur converts the joint into a simple antero-posterior hinge (Figs. 1 and 2). The cruciate ligaments are sacrificed but the lateral ligaments are preserved and these maintain stability of the new joint in an extended position though some lateral play is present in flexion as these lateral ligaments are relaxed in such a position. The size and shape of the prosthesis are calculated to ensure that the lateral ligaments are tight when the joint is extended.

The outer surface of the prosthesis, which is approximately the same width as the lower end of the femur, is a regular curve consisting of about three-quarters of a circle. The lower end of the femur is re-shaped into a tenon to fit into the mortise which constitutes the upper surface of the prosthesis, and a trifin nail attached to this passes up into the medulla of the femoral shaft to improve fixation. Additional later fixation should also be secured by new growth of bone into the transverse grooves cut in the anterior and posterior surfaces of the mortise. These, and transverse channels drilled across the body of the prosthesis, also serve to lighten the weight of metal. Three sizes of prosthesis provide fittings suitable for any adult knee. The trifin nail is tilted slightly from the vertical to correspond with the normal valgus tilt of the femoral condyles relative to the shaft as viewed in an antero-posterior direction, so it is necessary to have separate prostheses for right and left knees.

The lower articular surface of the femoral condyles is first excised by a transverse saw-cut distal to the upper attachments of the lateral ligaments after flexing the knee, excising the intercondylar structures and identifying the anterior margins of the lateral ligaments. A Perspex template applied to this cut surface is then used as a guide for the removal by saw and osteotome of the correct amount of bone from the anterior and posterior surfaces of the femoral condyles to produce an exact fit with the mortise of the prosthesis, the posterior cut passing behind the attachments of the lateral ligaments. The template is perforated for the introduction of a guide wire into the femoral shaft corresponding to the centre of the trifin nail of the prosthesis, which is thus guided into its correct position on the femur. First, however, the upper end of the tibia must be re-shaped into a concave surface to match the outer curved surface of the prosthesis, and this is done with a cranked osteotome of appropriate curvature.

FIG. 1.

FIG. 2.

Post-operatively gentle traction is maintained and mobilization starts after two to three weeks. The patient demonstrated had a painless range of 180–90 degrees (*see* Figs. 1 and 2) without crepitus, the knee was fully stable in extension, and she was able to walk, with some instability in the right hip but none in the left knee.

The President said that he supposed the arthroplasty had not been done long enough to test the bone reaction to weight bearing.

Mr. Mayer agreed and added that the earliest case he had was operated upon eight months ago; the case he had shown was six months after operation. From what one could see in the X-rays there was distinct sclerosis of the upper surface of the tibia. There was no suggestion of erosion or anything of that sort. It seemed to be hardening up.

The President said that he hoped Mr. Mayer would bring the patient along in five years.

Sinding-Larsen's Disease.—E. HENRIETTA JEBENS, F.R.C.S.

M. B., male, aged 12. First seen in January 1955, complaining of pain in both knees.

History.—In August 1954, while playing football, another boy fell against his knees hyperextending them. No pain at the time though he found it difficult to walk for a minute or two. No swelling was noticed after the accident, but he has had the pain since.

On examination marked tenderness over the lower poles of both patellæ was found. Nothing abnormal was found in the knee-joints. The general health of the boy was very good. X-rays (Figs. 1 and 2) showed irregular ossification at the lower poles of the patellæ, ? secondary centres of ossification. The left tibial tubercle showed a very small bony nodule which might be a mild Osgood-Schlatter's disease. Hip-joints were normal.

Comment.—This uncommon condition occurring in healthy, normal children between

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FIG. 1.—Lateral view of right knee.

FIG. 2.—Lateral view of left knee.

the ages of 10 and 14 is quite well known since Sinding-Larsen first described it in 1921. There is pain and tenderness over the lower pole of the patella following an indefinite history of trauma, often no more than the strains imposed on the knee-joints by an active child.

X-ray shows irregularity of contour of the inferior pole of the patella with a detached fragment of calcified tissue. The condition is often bilateral, though symptoms may only be present on one side, and is frequently associated with an Osgood-Schlatter's disease of the tibial tubercle. The diagnosis does not present any difficulty and the only treatment required is protection of the patella and its ligament, if necessary by plaster of Paris immobilization, until all symptoms have ceased and the X-ray shows fusion of the detached fragment with the patella. The ætiology is interesting. Sinding-Larsen regarded the condition as an epiphysitis similar to Osgood-Schlatter's disease, but this presupposes the presence of an accessory centre of ossification for the inferior pole of the patella which is not generally recognized by anatomists. But without such a centre the X-ray appearances are difficult to explain. An abnormal centre of ossification is a weak spot in the skeleton and will give rise to symptoms if subjected to an injury or repeated strain which would not affect a normal bone. A hereditary disposition to accessory centres of ossification would, therefore, predispose a child to this type of lesion and would also account for the frequent association with Osgood-Schlatter's disease.

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The following cases were also shown:

(1) **Patellectomy for Osteoarthritis in a First-Class Cricketer.**
(2) **Osteomyelitis Right Radius, Lower End.**—Mr. W. E. TUCKER.

Polyostotic Fibrous Dysplasia Complicated by Carcinoma of the Œsophagus.—Mr. J. V. DICKSON and Dr. W. W. RICHARDSON (for Mr. PHILIP WILES).

Progress Report on "True" or "Genuine" Congenital Dislocation of Left Hip.—Mr. R. H. V. HAFNER. (Previously shown February 2, 1954, *see* PROCEEDINGS, 1954, **47**, 454.)

Section of Anæsthetics

President—BERNARD JOHNSON, F.F.A. R.C.S.

[*March* 4, 1955]

Abnormal Response to Muscle Relaxants [*Condensed*][1]

By H. C. CHURCHILL-DAVIDSON, M.D., D.A.

THE term "muscle relaxants" has now come into common usage and embraces not only those drugs that act like *d*-tubocurarine (i.e. competitive inhibition or non-depolarization) but those which act in a similar manner to acetylcholine and bring about depolarization of the muscle-fibre: this group is represented by decamethonium (C.10) and succinyldicholine.

Recent findings in cases of myasthenia gravis suggest that this rigid classification into two distinct types is no longer strictly tenable, for both decamethonium and succinyldicholine give rise to a block having some of the characteristics of both groups. It has undoubtedly led to some confusion, and the purpose of this paper is to present a brief survey of relevant findings of the investigation into the effect of the muscle-relaxants on neuromuscular transmission in man.

Normal Neuromuscular Transmission

The chemical theory of normal neuromuscular transmission is now widely accepted. The basic concept is that on the arrival of an impulse at the end of a motor nerve, acetylcholine is responsible for bridging the gap between nerve and muscle fibre. These molecules excite the end-plate receptor on the fibre and trigger off a wave of depolarization which spreads along the fibre and brings about a mechanical contraction.

Methods of Study of Neuromuscular Transmission in Man

There are two main methods of studying neuromuscular block in man: (*a*) *Volitional activity*.—The muscle-strength of a conscious subject after varying doses of relaxants is recorded. The commonest method used is the measurement of hand grip-strength by squeezing a bulb attached to a column of mercury. Each determination requires the maximum possible effort on the part of the subject, which is sometimes difficult to obtain.

(*b*) *Electromyographic studies*.—The main nerve to a muscle, or group of muscles, is stimulated a variable number of times per second, and the resultant contraction of the muscle fibres is recorded either electrically or mechanically. The height of the action potential from peak to peak is taken as an index of the number of muscle fibres contracting. The synchronous contraction of 150–300 muscle fibres representing a motor unit gives rise to an action-potential similar to that recorded on the electrocardiograph. This method can be used on either conscious or anæsthetized patients, but the results obtained are not strictly comparable with those of volitional activity.

Neuromuscular Block

(1) *Deficiency block*.—Any factor that interferes with the liberation of acetylcholine is capable of producing a block of this type; for example, procaine (Harvey, 1939), botulinus toxin, and calcium deficiency act in this way. There is a failure of neuromuscular transmission but both the nerve and the muscle will respond to direct stimulation.

(2) *Depolarization block*.—The process is similar to that produced by acetylcholine in normal neuromuscular transmission but there is an increased duration and extent of depolarization. Succinyldicholine lasts only a few minutes because it is rapidly hydrolysed by the plasma into succinylmonocholine, which in turn is broken down to succinic acid and choline. In contrast, the action of decamethonium is prolonged because it is not hydrolysed *in vivo* but is excreted unchanged in the urine. A depolarization block due to either C.10 or succinyldicholine is preceded by muscle twitches, which represent the contraction of the muscle fibres before the onset of persistent depolarization and neuromuscular block. There are certain features of these fasciculations which are worth recalling:

Firstly, decamethonium produces a characteristic tightness of the jaw and calf muscles which occurs soon after the injection and may persist for many hours. Secondly, succinyldicholine leads to widespread fasciculations which are particularly prominent if the injection is given rapidly. Recovery is complete, but if the subject is ambulant after recovery a high proportion of cases (66%) will develop generalized muscle stiffness after moving about on rising the following morning. This stiffness is similar to that experienced by an untrained subject the morning after some violent exercise (Churchill-Davidson, 1954). Finally, electromyographically—using a recording needle deeply placed in a muscle—it can be shown that these twitches are not, as might be expected, single muscle-fibre potentials,

[1] The full paper will appear in *Anesthesiology*.

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but are full-action potentials, representing a whole motor unit of 150–300 muscle fibres contracting simultaneously. This might be taken as suggestive evidence of a central action of the drug, but the more likely explanation is that both succinyldicholine and C.10 stimulate a single motor end-plate which, in turn, by an anti-dromic reflex, fires off all the other fibres in the motor unit—the Masland-Wigton phenomenon (1940).

(3) *Non-depolarization block*.—This term is preferred to "competitive inhibition" because *d*-tubocurarine and decamethonium both compete with acetylcholine for the end-plate receptor. The distinctive factor is that curare combines with the receptor protein without causing depolarization; it simply prevents the acetylcholine from combining with the receptor, thereby stopping depolarization from taking place and producing a block of neuromuscular transmission. *d*-Tubocurarine, di-methylethyl-*d*-tubocurare, gallamine (Flaxedil), Laudolissin and Mytolon chloride act in this manner. If the concentration of acetylcholine can be raised, by inhibiting the action of cholinesterase with neostigmine or Tensilon, to a level at which the excitation threshold of the end-plate is reached, then the neuromuscular block is overcome.

(4) *Dual block*.—This type of block occurs in cases of myasthenia gravis and possibly—in certain circumstances—after the intravenous injection of decamethonium or succinyldicholine in normal subjects. The mechanism is complex and requires knowledge of the response of cases of myasthenia gravis to both *d*-Tubocurarine and decamethonium.

(*a*) *d*-Tubocurarine and myasthenia: Bennett and Cash (1943) were the first to suggest the injection of *d*-tubocurarine as a diagnostic test for the presence of myasthenia, based on the finding that some of these cases showed a hypersensitivity to the drug. A re-evaluation of this test has shown that only those muscles which are clinically weak have this hypersensitivity, whilst the other muscles will give a similar response to that of normal subjects. Consequently, respiratory paralysis is unlikely to follow a small test dose of *d*-tubocurarine unless the myasthenic patient has signs of weakness in the bulbar muscles.

(*b*) Decamethonium and myasthenia. To understand the response to decamethonium in patients with myasthenia gravis there are two findings in normal subjects which must be emphasized. First, the average normal subject shows a profound degree of muscular weakness after the intermittent injection of a total dose of 2·5–3·0 mg. C.10 over six minutes. Secondly, once this paresis is present an injection of an anticholinesterase—such as neostigmine or Tensilon—leads to a severe increase in the weakness.

In myasthenia the response to C.10 varies with the degree of myasthenic weakness already present. For example, a young girl (aged 21) who only had minimal myasthenic symptoms limited to her eyelids, showed no signs of paralysis even after the injection of 10 mg. C.10. Further studies suggest that if an even greater dose had been given the eyelid muscles would have been the first eventually to show signs of paresis. The fact that every motor end-plate showed resistance to the depolarizing activity of C.10 is evidence of the generalized character of this disease despite the fact that clinically it is only detectable in a limited group of muscles—in this patient, the eyelids.

At the other extreme, a severe case of myasthenia with generalized signs of weakness may show paralysis after the injection of as little as 1·0–2·5 mg. C.10. The failure of neuromuscular transmission, however, is *not* due to a block of the depolarization type but to one of non-depolarization (like *d*-tubocurarine); it is therefore readily reversible by neostigmine or Tensilon. There is also evidence that a brief period of depolarization precedes the change-over to this non-depolarization block (Churchill-Davidson and Richardson, 1953).

These two types of response to decamethonium—identical with that observed in myasthenia—have been described as occurring physiologically in various species of animals (Zaimis, 1952). Thus, whereas the muscles of the cat, bird, and frog respond to C.10 by pure depolarization, those of the monkey, dog, and hare can exhibit features not only of depolarization but also of non-depolarization block with this substance. In the light of this work it appears that the muscles of normal subjects respond to C.10 in a similar manner to those of the cat, whereas the myasthenic muscle-response resembles that of the dog.

The Abnormal Response

From time to time a case of prolonged action following the use of one of the muscle relaxants has been reported in the literature. Soon after the introduction of *d*-tubocurarine a number of cases of persistent apnœa were concluded to be due to "latent myasthenia", yet with the introduction of decamethonium and succinyldicholine the abnormal responses have continued to occur. The causes of prolonged apnœa in clinical anæsthesia are many and various, and they are not always associated with the use of a muscle-relaxant. The factors concerned fall naturally into two groups: (1) *Central action*.—An overdose of any anæsthetic drug, or a wide fluctuation in the plasma carbon dioxide level, depresses the activity of the respiratory centre and can lead to a prolonged apnœa.

(2) *Peripheral action*.—Again, the commonest cause of a prolonged response is probably

an overdose of the muscle-relaxant. The correct dosage will necessarily vary with the amount of muscle-tissue and the state of the circulation of the patient. A poor peripheral blood flow—such as often occurs at the end of a long operation—will be attended by a prolonged action of the drug. Similarly, delayed renal excretion, as in hypotension and hypothermia, theoretically could lead to a longer action, but this is not very evident in clinical practice. The fact that the diaphragm—the principal muscle of respiration—is always (except in myasthenia) the last muscle to become paralysed may well be due to the excellent circulation resulting from its constant exercise.

The administration of two drugs, both of which have a similar action on the neuromuscular junction, may lead to summation and a persistent apnœa. For example, a combination of ether and *d*-tubocurarine or decamethonium and neostigmine has been known to bring about this result.

Succinyldicholine, particularly when given as a continuous intravenous infusion, is apt to lead to a persistent apnœa or weak respiratory activity in the occasional case. As far as is known it is hydrolysed in two stages. First, one molecule of choline is quickly split off, leaving succinylmonocholine. In the second stage, which takes place more slowly, succinylmonocholine is hydrolysed to succinic acid and choline. The process of hydrolysis is controlled by the enzyme pseudocholinesterase. Thus, on the one hand, a low plasma cholinesterase level may lead to a slower breakdown to the monocholine derivative (Bourne *et al.*, 1952; Evans *et al.*, 1952). A low pseudocholinesterase activity is known to be associated with a number of factors, such as liver damage, undernutrition, cachexia and anticholinesterase drugs, but this may also occur in an otherwise apparently normal person (Calvert *et al.*, 1954).

On the other hand, succinylmonocholine, like its dicholine precursor, is capable of producing neuromuscular block if a sufficient concentration is reached: for animals this varies from 2·5–5·0 mg./kg. (Foldes *et al.*, 1954). On a molar basis the activity of the monocholine varies from 1/24–1/62 of the dicholine (Ellis *et al.*, 1953). Since the ratio of the molecular weights of the monocholine to the dicholine is 0·8, hydrolysis of 100 mg. of dicholine will lead to 80 mg. of the monocholine. Although it is unlikely that such a small amount of monocholine could have any effect, when doses of 1·5–2·0 grams are used then the accumulation of monocholine may be responsible for the prolongation of the paralysis.

Finally, the prolonged apnœa may be due to the presence of a dual block caused by either decamethonium or succinyldicholine. Although this type of response is rare, it must be seriously considered in view of the increasing number of reports in the literature of a prolonged paralysis—due to a depolarizing drug—which has been completely and rapidly reversed by the injection of an anticholinesterase drug (Hodges, 1953; Grant, 1952; Ruddell, 1952). The presence of a dual block due to a depolarizing drug is known to occur in cases of myasthenia gravis; it is therefore possible that the end-plate response of normal subjects may change under persistent bombardment from one of pure depolarization to one of dual response.

Diagnosis of the Abnormal Response

If we are to make any progress in the diagnosis of the rare case of prolonged apnœa following the use of one of the muscle relaxants it is important that some attempt be made to isolate the causative factor during the period of paralysis. Electrical stimulation of a main nerve trunk will reveal whether the peripheral musculature is capable of a contraction: this will help to distinguish cases of central or respiratory centre depression from those due to causes affecting the neuromuscular junction. Blood samples can be used to estimate the carbon dioxide tension and the plasma-cholinesterase level. Finally, an intravenous injection of 10 mg. of Tensilon will help to elicit the possible presence of a dual block. Tensilon is used—in preference to neostigmine—because it acts for only a few minutes, and were the block one of pure depolarization then it would be potentiated briefly, whereas a dual block would be completely reversed.

Summary

There are, therefore, three types of neuromuscular block that may be encountered in man: (1) Depolarization; (2) Non-depolarization; and (3) Dual block. This last type of block occurs in cases of myasthenia gravis, and possibly—in certain circumstances—in normal subjects after a depolarizing drug has been given. The possible causes of prolonged apnœa following one of the muscle relaxants are reviewed and some suggestions to aid in the diagnosis of this condition are made.

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Dr. H. O. J. Collier: Dr. Churchill-Davidson has pointed out that movement after recovery from succinylcholine is likely to bring on muscle-pains. Such movement would, of course, inevitably depend on release of acetylcholine at the motor end-plates of the muscles concerned. We know from the work of Professor C. A. Keele and his colleagues that dilute solutions of acetylcholine readily cause pain at the exposed site of a blister. I wonder therefore whether the acetylcholine itself released during movement is one factor in causing muscle-pain after succinylcholine. Some light might be thrown on this question by studies of the results of succinylcholine in E.C.T., in which movement might be suppressed (except in muscles stimulated directly by the electrodes) but acetylcholine would presumably be liberated at the motor end-plates in abundance.

Dr. Geoffrey Organe drew attention to the existence of a fairly wide variation in response of normal subjects to decamethonium. He quoted the case of a patient who opened his eyes a few minutes after the administration of 0·5 gram of thiopentone and 5 mg. of decamethonium, followed by nitrous oxide and oxygen.

Dr. T. Cecil Gray expressed great interest in the findings of Dr. Churchill-Davidson in regard to the reactions of muscles in myasthenic patients. If Dr. Churchill-Davidson's findings were correct it would seem that the "non-myasthenic" muscles in these patients proved an exception to the general rule that muscles which were sensitive to agents acting by non-depolarization block were resistant to those acting by depolarization and vice versa. These results showed that these "non-affected" muscles were resistant to decamethonium—a depolarizing drug—but *not* sensitive to *d*-tubocurarine, a non-depolarizing drug. Dr. Churchill-Davidson had not clearly indicated the experiments he had carried out to determine that these muscles were, in fact, not sensitive to *d*-tubocurarine. It would be hazardous, in his opinion, to jettison the test dose when using non-depolarizing relaxants because of Dr. Churchill-Davidson's findings. Even if it were a fact that the "non-myasthenic" muscles in myasthenic patients did not show sensitivity to these drugs, nevertheless there was ample evidence, not only in the experience of many anæsthetists but also in the literature, for the fact that test doses revealed patients who were hypersensitive—although not necessarily myasthenic.

Dr. Hermann Lehmann: As one who has worked on the relation between pseudocholinesterase level and response to succinyldi- and succinylmono-choline I should like to say that pseudocholinesterase of the plasma is only one of the factors involved in the regulation of this response and we cannot expect that all cases of apnœa following the administration of these methonium compounds are due to low pseudocholinesterase. Even if a low pseudocholinesterase is responsible for such an apnœa it may only start this condition and other factors will take over. Certainly simple pseudocholinesterase deficiency alone cannot cause more than a twenty minutes' apnœa and a prolongation of the condition indicates that other influences are at play.

We have seen at St. Bartholomew's Hospital a number of incidences where people were resistant to succinyldicholine. We examined the succinyldicholine both by chromatography and by injection into rabbits and found that it was active and Dr. N. G. P. Butler, the anæsthetist then working at St. Bartholomew's Hospital, was struck by the fact that the individuals were all being operated on for toxic goitre. Their pseudocholinesterase levels were at the higher limit of normal, about 120 to 130 units. This may, of course, be an indication of yet higher levels in the tissues. We examined a number of individuals suffering from toxic goitre but could not always find a particularly high pseudocholinesterase level and we abandoned this line of investigation. However, Professor R. H. S. Thompson and his colleagues, investigating hyperthyroidism from a different point of view, have recently reported that there is an overall increase of pseudocholinesterase level in this condition.

Dr. R. P. Harbord approved the suggestion that in patients with a prolonged apnœa the blood CO_2 tension should be determined. Since this entailed pH and manometric CO_2 content measurements on arterial blood, anaerobically withdrawn, he asked Dr. Churchill-Davidson if he thought it would be a more practical procedure to measure the CO_2 tension of the patient's "alveolar" gases.

Dr. Victor Goldman referred to the possibility of an abnormal response due to the formation of succinylmonocholine when large quantities were employed of the short-acting succinyldicholine. He had never experienced it even though he had used on many occasions a gram or even more in the form of a drip. In fact the rapid return of the normal respiratory rhythm after a long abdominal operation was one of the most striking features of the drip technique. What Dr. Goldman felt was a greater danger was the synergistic action of the depolarizers with procaine (Foldes *et al.*, 1953, *Science*, 117, 383) and he asked Dr. Churchill-Davidson if he had any knowledge of the action of the short-acting muscle relaxants in the presence of high blood levels of procaine penicillin. This was an important point as so many patients to-day were operated upon under cover of a procaine penicillin "umbrella".

Dr. Churchill-Davidson, in reply, said, that five myasthenic patients had failed to reveal marked sensitivity to *d*-tubocurarine in their unaffected muscles. On the basis of Dr. Gray's "rule of opposites" one might expect the young girl mentioned above to be extremely sensitive in these muscles. This was not the case.

Section of Endocrinology

President—P. M. F. BISHOP, D.M., M.R.C.P.

[*March* 23, 1955]

ADDISONIAN CENTENARY MEETING AT GUY'S HOSPITAL, LONDON

ON March 23, 1955, by kind invitation, the Section met at Guy's Hospital Medical School in celebration of the centenary of the publication of Addison's monograph entitled "On the Constitutional and Local Effects of Disease of the Suprarenal Capsules". After being entertained to lunch members were shown specimens in the Museum from Addison's patients. The President opened the afternoon's proceedings by giving a short account of Addison and his work at Guy's Hospital.

The Pathology of the Adrenals, Thymus and Certain Other Endocrine Glands in Addison's Disease: an Analysis of 37 Necropsies

By J. C. SLOPER, M.D., M.R.C.P.

ALTHOUGH the various pathological changes which may affect the endocrine glands in Addison's disease are fairly well recognized, it is difficult to extract from the literature evidence of their incidence and severity. Yet, with progress in substitution therapy and with the newer methods at our disposal for the recognition of disturbances in endocrine function, such information is of increasing value. Accordingly, the pathological changes present in adrenals, thymus, pancreas, pituitary and thyroid have been reviewed in material available from a series of 37 necropsies performed on cases of Addison's disease at the London Hospital between 1912 and 1951. The purpose of this analysis is to evaluate the extent to which these various glands are affected in Addison's disease; attention will also be drawn to those aspects of the pathogenesis of these changes which are still obscure; and it will be shown that there are differences between the pathology of idiopathic and tuberculous Addison's disease which may prove of value in the clinical differentiation of these conditions.

In this series the diagnosis of Addison's disease rests primarily upon the presence in 15 cases, 9 women and 6 men, of idiopathic atrophy of the adrenals, and in 22 cases, 9 women and 13 men, of granulomatous and fibrocaseous tuberculosis of the adrenals: in both groups most cases died between their twentieth and fiftieth years. In none of the idiopathic group was there the simple atrophy of the adrenals characteristic of Simmonds' disease (Crooke and Russell, 1935); Simmonds' disease was also excluded in all save 3 of these cases by the macroscopic examination of the pituitary. Evidence of buccal and cutaneous pigmentation was present in nearly every case, and in retrospect there was nearly always evidence of asthenia, abdominal disturbance and hypotension. Associated endocrine disorders such as myxœdema and hypopituitarism were not diagnosed, but one case presented with severe hypoglycæmia only to develop diabetes mellitus (Simpson, 1932). Active and progressive tuberculosis was present elsewhere in the body in 3 cases of the first group; in 7 there were small fibrocaseous pulmonary lesions, while in the remainder similar lesions were scarred and obsolete. In 5 of the 15 idiopathic cases there were tuberculous lesions in these last two categories. The average duration of the disease, a figure difficult to assess, was thirteen months in the idiopathic group and twelve in the tuberculous. Treatment varied greatly, but the 2 cases with longest survival, 1 tuberculous and 1 idiopathic, survived sixty and forty-eight months respectively. Both were given Eucortin in their last six months but otherwise received no specific treatment.

Histories of this duration are probably explained by the fact that in many cases there was a moderate amount of surviving cortical tissue. This is reflected by the variation encountered in the weight of the adrenals in idiopathic Addison's disease, namely between 1·9 and 4·6 grams in 11 instances (average 2·7 grams). The lowest figure is a rough measure of medulla and condensed connective tissue, so that from the uppermost figure it can be deduced that there was as much as 2·7 grams of surviving cortex. The corresponding average weight of cortical tissue in Simmonds' disease deduced from data reviewed by Sheehan (1939) would be rather higher, namely 3·6 grams. Weight for weight, however, less hypofunction might be expected in Simmonds' disease, since the cortex retains its zonal pattern and is uninflamed. Conversely in our cases of Addison's disease the cortex was characteristically composed of groups of large cells somewhat resembling hepatic

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regeneration nodules. There was a moderate and variable lymphoid infiltration. This always in slight degree affected the medulla also, which, however, appeared otherwise normal. Such "fibrosis" as was present I would ascribe merely to a condensation of connective tissue. The vessels were normal save in 3 female cases in each of which an artery was somewhat narrowed by what was probably organized thrombus. In 2 other cases there were small focal deposits of hæmosiderin in the cortex.

These changes are to be contrasted with those found in the tuberculous adrenals, where the gland was usually enlarged by a fibrocaseous lesion in which surviving islands of cortex were scanty and medulla difficult to identify with certainty (Table I). It is unlikely that

TABLE I

		Adrenal Medulla			Adrenal Cortex	
	Cases	Nil	Scanty	Normal	Moderate	Very scanty	Nil
Idiopathic atrophy..	15	0	0	15*	9	6	0
Tuberculosis ..	22	18	4	0	6	7	9

*There was always a slight to moderate lymphocytic infiltration of the medulla.

this apparent difference in the amount of surviving cortical tissue was entirely due to the greater amount of tissue which required to be examined in the enlarged tuberculous adrenal. It would be reasonable therefore on morphological grounds to expect a greater diminution in cortical, and more particularly in medullary, function in tuberculous than in idiopathic Addison's disease.

The pathogenesis of these lesions is still in part obscure: for our understanding of the pathogenesis of the idiopathic lesion has not been advanced since Wells (1930) likened it to acute yellow atrophy of the liver. Evidence of some acute episode of necrosis or hæmorrhage (Crawford, 1951) was not obtained from the histories of any of these cases.

The thymus (Table II) was next examined to determine whether it would provide an

TABLE II.—THYMIC GLANDULAR (LYMPHOID) TISSUE

	Cases	Normal	Up to twice normal maximum	Over twice normal maximum
Addison's disease ..	18	11 (11) (11)	6 (7) (6)	1 (0) (1)
Thyrotoxicosis ..	34	13 (13) (11)	11 (11) (10)	10 (10) (13)

Figures in brackets allow for 10% overestimates and underestimates of weight of thymus.

Thymic weights in Addison's disease were:

16–20 years	20·4 and 14·3 grams ($\frac{3}{4}$ and entirely glandular)
21–25 years	36·7 and 23·6 grams (entirely and $\frac{3}{4}$ glandular)
26–30 years	17, 23·8, 16·3 and 31·1 grams ($\frac{1}{2}$, $\frac{3}{4}$, $\frac{1}{4}$, $\frac{3}{4}$ glandular)
31–35 years	20·7, 23·1, 24·3, 12·4 grams ($\frac{1}{2}$, $\frac{3}{4}$, $\frac{1}{4}$, $\frac{3}{4}$ glandular)
36–45 years	13, 2·9, 22·9, 28·2, 16·9 grams ($\frac{1}{2}$, 0, $\frac{1}{4}$, $\frac{3}{4}$, $\frac{3}{4}$ glandular)
47 years..	11·2 grams ($\frac{3}{4}$ glandular)

index of residual adrenal function, for it is recognized that in animals the thymus enlarges after adrenalectomy (Jaffe, 1924). However, satisfactory information concerning the thymus in Addison's disease, that is data including the weight of the gland and some indication of the amount of glandular (lymphoid) tissue, is confined to 2 cases described by Hammar (1929), in 1 of which there was hypertrophy. The necessary data were available in 18 cases of the present series and in 34 necropsies performed between 1927 and 1932 on cases diagnosed clinically as thyrotoxic. The proportion of glandular tissue was assessed in microscopic preparations and from this and the weight of the whole gland the "weight" of glandular tissue was estimated. Two unjustified assumptions were made, first that the sections examined were representative of the whole gland, and second that connective and adipose tissue and lymphoid tissue were of the same specific gravity. These data, when compared with Hammar's (1926) for the normal thymus, corroborated his finding (1929) that there was a gross and frequent increase in the "weight" of glandular tissue in thyrotoxicosis. There was, however, no comparable tendency in Addison's disease although in 7 of 18 instances the glandular tissue was increased in amount. Indeed, it is of interest that the whole thymus was never of abnormal weight. As for the hyperplasia of lymphoid tissue which has been said to occur throughout the body in Addison's disease, the difficulties in assessing this have been discussed elsewhere (Young and Turnbull, 1926), and no conclusion could be reached in this series.

This is not to deny that there may be in Addison's disease a tendency towards thymic hypertrophy, perhaps concealed by factors such as infection causing accidental thymic involution. The alternative view is that thymic hypertrophy is infrequent in Addison's disease. The absence of this change might then be an indication of residual adrenal function. Evidence on this point was equivocal in our series, for there was no good morphological correlation between the amount of surviving cortical tissue and the "weight" of the thymic glandular tissue. Indeed, if the latter is any guide to adrenal function, then the fact that in 26 of 34 thyrotoxic cases the adrenals were of normal weight by Castaldi's standards (Castaldi and Vanucci, 1927) suggests that the morphology of the adrenal is a poor index of its function. In 6 of the remaining 8 thyrotoxic cases the adrenals were slightly enlarged, and in 1 of these the thymic glandular tissue was increased. In 1 of 2 cases with small adrenals thymic glandular tissue was also increased.

With regard to the pancreas, it has recently been claimed that there is invariably an islet-cell hyperplasia in Addison's disease (Hinerman, 1951), an interesting observation in view of the tendency of patients to develop hypoglycæmia. However, the examination of the pancreas in 16 of our cases failed to confirm Hinerman's findings, although in 2 idiopathic cases there were small islet-cell adenomata, tumours hitherto unrecognized in this condition (Sloper, 1954). In general the pancreas tended to be diminished in weight, and once, in the presence of diabetes, was undoubtedly atrophic.

The pituitary was examined in 18 instances, 5 of which were originally used for differential counts, following Rasmussen, by Crooke and Russell (1935). In the remaining 13 instances similar counts were performed, but on one section only instead of three. In 7 instances only sagittal sections were available. The whole series, with these severe limitations, nevertheless corroborates Crooke and Russell's findings. There was a marked fall in basophils, and a lesser although definite fall in acidophils (Table III). Indeed, were it possible to

TABLE III.—ANTERIOR LOBE OF THE PITUITARY GLAND

		Acidophils	Basophils	Chromophobes
Idiopathic atrophy ..	7 (3 sagittal)	Low	Low	High
Tuberculosis	11 (4 sagittal)	Low 10 Low-normal 1	Low	High

show that lymphoid atrophy of the adrenal, like lymphoid atrophy of the thyroid, can occur in Simmonds' disease, then it might reasonably be suggested on morphological grounds that in idiopathic Addison's disease the primary dysfunction lies in the pituitary. Certainly the tendency towards panhypopituitarism suggested by the fall in both basophils and acidophils indicates a need for broadening of the scope of substitution therapy. There is, however, evidence consistent with great pituitary activity in Addison's disease: for in untreated patients, unlike normal persons, ACTH can be found in the blood (Paris *et al.*, 1954), evidence which indicates a discrepancy between the morphology and function of the pituitary in Addison's disease. With regard to the pathogenesis of these pituitary changes, it seems to be held that they are secondary to the adrenal dysfunction; but they have yet to be reproduced in their entirety in the adrenalectomized animal.

Little attention has been paid to the neurohypophysis in Addison's disease. Now, adrenalectomy in the rat (Malander and Corbetta, 1953; Cavallero *et al.*, 1954) leads to the loss of stainable "neurosecretory" material from the posterior pituitary. This material is held to represent either posterior pituitary hormone or a bearer substance for this hormone. Accordingly, since there is a diminution in water-diuresis in Addison's disease (Homer Smith, 1951), it seemed profitable to examine the distribution of hypothalamic and posterior pituitary "neurosecretory" material in this condition. In the single case so far studied this stainable material appeared normal in amount.

TABLE IV.—THE THYROID

	Cases	Normal	Abnormal involution	Simple atrophy
Tuberculous	10	7	2	1
Idiopathic	11	3	7	1

With regard to the thyroid (Table IV), it is important to note that in 10 of the 21 glands studied (Sloper, 1953) no definite pathological change was found, although in a number of instances there was a slight and variable lymphoid infiltration, a lesion which is in fact a normal finding in patients after the fifth decade. In 9 instances, 7 in idiopathic Addison's disease, the gland was either abnormal or probably abnormal, while in 2 instances the gland showed

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slight simple atrophy. Characteristically the severely affected gland, although of normal or diminished weight, was similar in other respects to the goitre found in Hashimoto's disease. This form of accelerated lymphoid involution, although not accompanied in our series by overt myxœdema, may in future be capable of clinical recognition, and may thus help in the recognition of idiopathic Addison's disease, with which it is usually associated. This lymphoid infiltration, like thymic hyperplasia, has been attributed directly to adrenal cortical hypofunction. However, in our series the association between thymic hyperplasia and lymphoid changes in the thyroid was probably fortuitous. Thus sections from thymus and thyroid were available in 17 instances: in 7 the thyroid was abnormal, and in 4 of these the thymic glandular tissue was increased: but in 3 of 10 cases with normal thyroids the thymic glandular tissue was also increased. Indeed, since a lymphoid infiltration commonly accompanies age-involution of the thyroid, it seems simpler to regard this infiltration merely as one aspect of accelerated involution of the thyroid and perhaps hypopituitary in origin. This lymphoid involution has not been reproduced in the adrenalectomized animal.

This analysis of post-mortem material thus reveals that, although the adrenal and pituitary are constantly affected in Addison's disease, pathological changes in thyroid, thymus, and pancreas are variable and inconstant. Particular attention is drawn to the presence in all the pituitaries examined of morphological changes consistent with a tendency towards hypopituitarism; to the presence in about a half the thyroids examined of a tendency towards involution; to the absence in many instances of evidence of thymic enlargement; and to the presence in two cases of small pancreatic islet-cell adenomata.

The pathogenesis of most of these lesions is still obscure, and this is true also of those affecting the adrenal in idiopathic Addison's disease. In the study of the pathogenesis of the extra-adrenal lesions it is clear that one obvious difference between the patient and the adrenalectomized animal should not be neglected, namely the frequent survival in the former of a variable amount of cortical and medullary tissue.

With regard to the differentiation between idiopathic and tuberculous Addison's disease, it is difficult to analyse the pathology of these conditions without feeling that it may be possible to distinguish them in life. The matter is of practical importance since there is the possibility that cortisone therapy may activate a tuberculous lesion. Further, it has been held (Sorkin, 1949), although this was not particularly apparent in this post-mortem series, that idiopathic Addison's disease has a better prognosis than its tuberculous counterpart. The distinction cannot be made on age or sex incidence: again radiological evidence is inconclusive, for as Rowntree and Snell (1931) stated, adrenal calcification is not common in tuberculous Addison's disease. The presence of active and extensive tuberculosis elsewhere in the body certainly favours a tuberculous ætiology. This, however, was the exception in our series, and in general extra-adrenal tuberculous lesions were small and quiescent and occurred also in idiopathic Addison's disease. It is suggested therefore that further points of distinction should be sought, first in the greater tendency towards involution of the thyroid encountered in idiopathic Addison's disease; and second in the greater destruction of adrenal tissue, and in particular of medullary tissue, encountered in tuberculous Addison's disease.

My thanks are due to Professor Dorothy Russell for help in the preparation of this paper.

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Biological Effects of Aldosterone with Especial Reference to Man

By F. T. G. PRUNTY, M.A., M.D., F.R.C.P., R. R. MCSWINEY, M.B., B.S.Lond., and IVOR H. MILLS, M.B., B.Chir., M.R.C.P.

ALDOSTERONE is the most recently discovered natural product of the adrenal cortex, and it seems it represents a very significant part of the activity of the old so-called amorphous fraction of adrenal extract obtained as a residue by Kendall and others after separating out the crystalline materials. The isolation, which sprang from the foundations laid by Drs. Simpson and Tait at the Middlesex Hospital, was greatly facilitated by the sensitivity of the rat to this substance (or electrocortin as it was originally called) in respect of sodium reabsorption by the kidney tubule. It is almost by definition therefore that aldosterone is a powerful sodium-retaining substance. It thus became important to determine in what other way it showed biological activity. Since a wide range of methods in the general field of adrenal physiology were already to hand, advances in this direction have been extremely rapid and comprehensive in spite of severe limitation set by the difficulties and cost of the isolation procedures for aldosterone. For instance about 5 mg. comes from 100 kilograms of beef adrenals (Wettstein, 1954). The work to be described in the present paper has been carried out with the use of 12·5 mg. of aldosterone kindly supplied by the Ciba Co. of Basel, through the courtesy of Dr. F. Gross.

At the time of commencement of this work observations in man had been very restricted. Mach *et al.* (1954) had reported on the administration of aldosterone to 2 patients with Addison's disease for a total time of eleven days and made a careful study of the metabolic effects. Simpson and Tait (1955) had described the effect of aldosterone on the salivary Na/K ratio in normal persons and a patient with Addison's disease. The greater part of our general knowledge has, of course, come from animal experiments, since for these much smaller amounts of hormone are required. Maintenance of the adrenalectomized dog in a satisfactory state demonstrated the life-saving properties of this substance under these conditions (Gross and Gysel, 1954). These authors and Spiers *et al.* (1954) also observed that it was one-half to one-third as active in depressing the eosinophil count of adrenalectomized mice. At about the same time Schuler *et al.* (1954) in Switzerland found that it was about one-third as potent as cortisone in causing the deposition of glycogen in the mouse liver, requiring 100 μg. per mouse to cause a 200% rise in glycogen content.

The present paper summarizes the effects of aldosterone administration to 8 patients.

Our investigations began with the confirmation of the therapeutic effect in Addison's disease. In our first patient (E. W.), after complete withdrawal of therapy, administration of aldosterone in doses of 200 μg. for three days and 400 μg. on the last two days checked and even reversed the metabolic changes and weight loss thus ensuing. Clinically the patient was in excellent shape during this short period of replacement of conventional treatment by aldosterone, which during this time had little effect on blood pressure and no noticeable effect on pigmentation which Mach *et al.* (1954) and Soffer (1955) had found to be improved.

There was in this patient a considerable diuresis and natriuresis on withdrawal of therapy possibly due to some previous overtreatment (Prunty *et al.*, 1954). This may to some extent have favoured the very considerable retention of sodium and chloride promoted by aldosterone. It must be noted that sodium was retained in excess of chloride, suggesting the possibility of intracellular transfer of some 130 mEq. of sodium. Potassium balance was not, in this individual, strikingly affected. It was also noted that there was a significantly more positive water balance, accompanied by a check in the fall and even a slight rise in weight. Further observations were made on a girl with adrenal hyperplasia leading to pseudohermaphroditism (M. W.) (*loc. cit.*). These exactly confirmed this picture in all respects, but there was, in addition, a significant change in potassium balance involving a considerable rebound retention. The dosage of aldosterone given to this individual was somewhat greater, being 500 μg. the first day and 1050 μg. the next two days. The change in the ratio of K/Na is perhaps the most sensitive index of the effect of aldosterone on urine electrolyte excretion. In this patient in a twenty-four-hour urine sample it reached a peak of 1·8. The water balance appeared to become more positive. It was pointed out at the time that there was a great falling off in sodium retention and the K/Na ratio when 750 μg. of aldosterone were given intravenously over a twenty-four-hour period immediately at the conclusion of the intramuscular series of doses. The administration of aldosterone to these patients led to changes in the serum electrolytes which were difficult to interpret in E. W., but it is noteworthy that there was a persistent fall in serum chloride level during the period of aldosterone administration. In the second patient there was expected rise in serum sodium accompanied by a fall in hæmatocrit level. Comparison of the effects of aldosterone with those of cortisone in doses of 75 to 100 mg. showed that with the latter retention of sodium and chloride over an eight-day period was very small in comparison with the changes seen

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with the large doses of aldosterone, although the effects on potassium excretion were greater. The nitrogen balance did not show that this was due to increased protein breakdown induced by cortisone, but this effect may have been counterbalanced by the endogenous over-production of androgen from the hyperplastic adrenal cortex. This recalls the poor ability of cortisone to cause sodium retention previously observed in Addison's disease, (Prunty *et al.*, 1954). Aldosterone did not increase nitrogen excretion in either of these patients.

More detailed comparison of the effects of aldosterone administered by different routes has been made (Prunty *et al.*, 1955). The technique adopted was to observe the effects of single doses on patients on a balanced regime. Each observation day alternated with a control day. Treatment was withdrawn from the Addison's patients. The dose given was usually 250 μg. Intravenous administration was at a uniform rate in 500 ml. 2·5% glucose over a five-hour period. The data on the duration of action by the intramuscular route were confirmed. In a second Addisonian (P. M.) and a gastric ulcer (C. T.) approximately 30 mEq. of sodium were retained in twenty-four hours. The peak K/Na ratio was approximately 4, occurring in the third to fifth hour period. Intravenous infusion was somewhat less effective and oral dosing least so, in one experiment having no effect on the K/Na ratio.

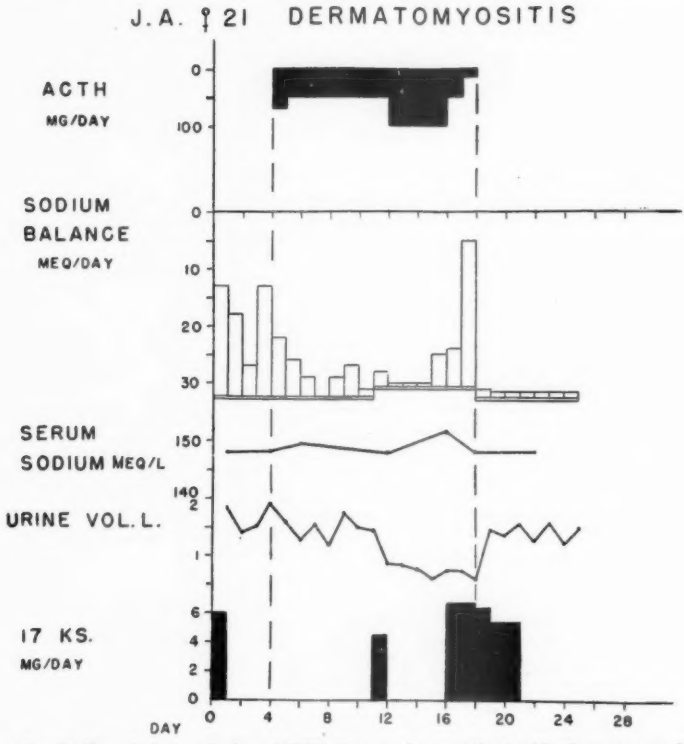

FIG. 1.—Sodium balance during ACTH therapy in a patient with dermatomyositis. Note very large retention after stopping ACTH.

In a third Addisonian (V. C.) 225 μg. of intravenous aldosterone produced good sodium retention, comparable with the intramuscular responses previously observed but somewhat less than the response from 5 mg. of DCA. Potassium loss was also considerable under these conditions with aldosterone, rising from control levels of 40 μEq. per minute to 100 μEq. per minute at the end of the infusion. The DCA had less effect on potassium excretion.

Observations on water excretion have shown that the abnormal diurnal rhythm of Addison's disease is not corrected nor is the capacity for normal diuresis restored (Prunty *et al.*, 1954). There was slight but definite evidence of water retention in patients I. W. and M. W. In patient P. M. the normal urine flow was halved. This is of importance

since Gross and Gysel (1954) suggested that unlike DCA aldosterone had little effect on water retention and it might be hoped that water overloading could be avoided. Our findings are consistent with those of Ward *et al.* (1954) who found significant rapid weight gain in patients with rheumatoid arthritis and of Thorn (1955) in an Addisonian receiving 1 mg. daily for seven days.

We have observed no effect of aldosterone at any time on *eosinophil counts*, even after 1 mg. doses. Careful review of the data published on sugar metabolism (Kekwick and Pawan, 1954; Mach *et al.*, 1954; Prunty *et al.*, 1954) shows the changes observed were inconstant. To investigate the position further the effect of aldosterone on the fasting blood sugar and insulin tolerance in a patient with Addison's disease (G. D.) and a patient adrenalectomized for prostatic carcinoma (H. T.) was investigated. No increase in the fasting blood sugar levels was observed and no decrease of the sensitivity to insulin (Prunty *et al.*, 1955). This leads us to revise our previous opinion about the effects of aldosterone doses up to 1 mg. on carbohydrate metabolism in man, and makes us think there is no significant effect. This is consistent with the failure to observe depression of ketosteroid excretion in the patient with adrenal hyperplasia (M. W.) with doses of this magnitude.

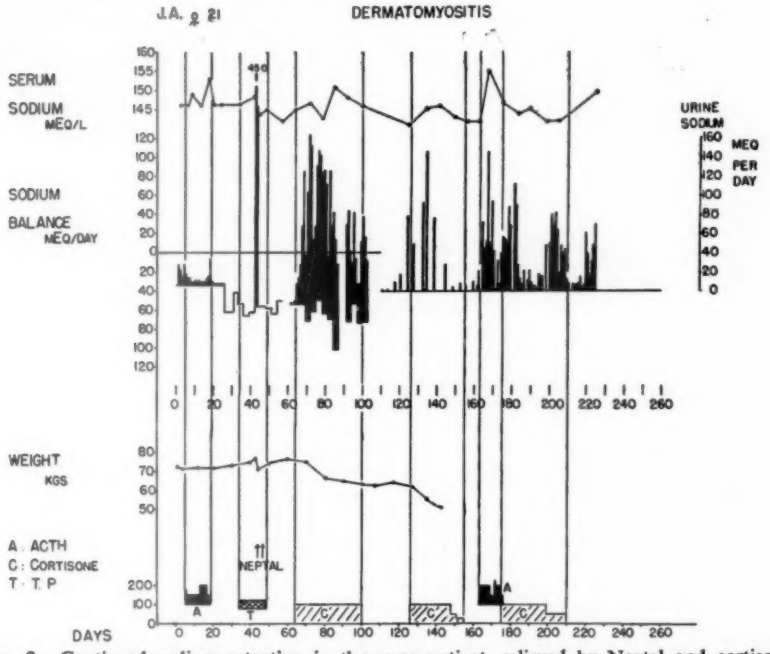

FIG. 2.—Continued sodium retention in the same patient, relieved by Neptal and cortisone. Note the period from day 0–15 is the same as that in Fig. 1. On day 110 the "balance" was discontinued and the figures represent urine sodium excretion.

[Figs. 1 and 2 are reproduced from *Proceedings of the Tenth International Congress of Dermatology*, London, 1952 (Prunty, 1953) by kind permission.]

We should like to turn now to a more speculative note and discuss some findings made several years ago in a patient with dermatomyositis (Prunty, 1953). This patient was treated with ACTH in doses up to 100 units daily for fourteen days in an acute phase of the disease (Fig. 1). The expected change in sodium balance occurred, namely considerable sodium retention which diminished on reduction of the dose of ACTH. On the day after withdrawal of ACTH sodium excretion suddenly *decreased* to 1 mEq. per day or less and despite an intake of 30 or more milli-equivalents per day remained at this low level until cortisone was given on day 60 and returned after its withdrawal on day 100 (Fig. 2). The pathological retention was relieved by Neptal, cortisone and ACTH. Three days after Neptal injection, despite elevation of K intake, the serum potassium level was only 2·35 mEq./l. Potassium balance data during this phase showed the patient to be in strongly negative

balance. These findings recall those of Conn (1955) in a patient with an adrenal tumour and excessive aldosterone excretion in the urine. They raise the possibility that the ACTH administration might have "triggered off", perhaps together with the low Na intake, the secretion of aldosterone, the action of which was opposed by cortisone. The precise relationship of aldosterone secretion to ACTH stimulation is still obscure. The failure of diminution of steroid excretion in the girl, M. W., given aldosterone is against an ACTH dependence, but possibly the dose of aldosterone may have been too little. The experiments of Cope and Garcia-Llaurado (1954) and of Axelrad *et al.* (1954) seem to indicate that aldosterone production is ACTH independent. However, the recent report of Singer and Stack-Dunne (1955) working with rats, shows that, in this animal at least, ACTH plays a part in stimulating aldosterone secretion, although the physiological mechanism seems more complicated. It still seems to the authors that in man the very strong sodium-retaining effects of ACTH require the participation of a "mineralocorticoid" in the response.

Summary.—Aldosterone may be used as replacement therapy in Addison's disease in doses up to 200 μg. daily. The duration of action is short and most pronounced by the intramuscular route. It causes intense Na retention and some potassium excretion in these doses with a large change in urine K/Na. It seems to cause intracellular transfer of Na and shift of water from cells to interstitial fluid as does DCA. It is approximately 25 times as active as DCA. Water retention is produced but not normal water diuresis in an adrenal-deficient patient. It seems to lack the carbohydrate corticoid effects of cortisone in doses up to 1 mg.

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Section of Comparative Medicine

President—Sir WELDON DALRYMPLE-CHAMPNEYS, Bart., M.A., D.M., F.R.C.P.

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DISCUSSION ON SOME DISEASES OF PETS TRANSMISSIBLE TO MAN

Professor S. P. Bedson:

Psittacosis

It has been realized for some eighty years now that birds of the parrot family suffered from an infectious disease to which man was susceptible. For a long time the evidence in support of this belief was solely epidemiological but proof was provided when during the pandemic of 1930, the same infective agent was isolated from both human and psittacine cases of the disease. This agent is a large basophilic virus belonging to the psittacosis-lymphogranuloma group which modern practice places with the rickettsiales.

Natural host range.—One of the most important advances in our knowledge of this group of closely related viruses concerns their natural host range. In 1930 it was believed that the natural hosts of psittacosis virus were confined to the order psittaciformes. It was known that other birds were susceptible, the canary and the Java sparrow for instance, and that human infections might be derived from such non-psittacine sources. But this did not seem to conflict with the conception of psittacine birds as the sole natural hosts since infection in non-psittacine birds could usually be traced to parrots in bird shops or pet stores. This belief was short-lived. A severe form of atypical pneumonia occurring in the late summer and confined very largely to middle-aged women which had made its appearance in the Faroe Islands was thought to be psittacosis and to have its origin in the newly fledged fulmars which the natives caught and used for food. This was confirmed by Haagen and Mauer (1938) when they isolated psittacosis virus from both fulmars and the affected Faroese. Two years later Pinkerton and Swank (1940) showed that a fatal disease which developed in some of their experimental pigeons on a thiamine-deficient diet was due to a virus of the psittacosis group, and the same year Coles (1940) of Onderstepoort in South Africa found infection with a psittacosis virus in a pigeon flock. Since that time the avian host range of the psittacosis viruses has been progressively extended so that to-day at least seventy species of birds belonging to ten orders, including the psittaciformes, are known to be susceptible. In addition, infection with related viruses has been found in several species of mammal; these include the virus of mouse pneumonitis (Nigg, 1942; Gönnert, 1942), the virus of cat pneumonia (Baker, 1944), the virus of enzootic abortion of ewes (Stamp, *et al.*, 1950), a virus isolated from the intestinal tract of calves (York and Baker, 1951), one found causing disease in opossums (Roca-Garcia, 1949) and the virus of sporadic encephalomyelitis of cattle (Wenner, *et al.*, 1953).

Interrelationship of the viruses of the psittacosis group.—The question now arises as to the relationship of these viruses commonly referred to as belonging to the psittacosis group. Similarity in size and staining affinities and the facts that they pass through the same sequence of developmental forms when multiplying and share an antigen in common undoubtedly indicate a relationship. But there are other tests which can be applied to this problem: experimental host range, infectivity by different routes in the same animal—the mouse and pigeon in particular—neutralization tests made with sera prepared in the domestic fowl and toxin-antitoxin neutralization tests. The evidence which these tests has provided suggests that the avian strains are more nearly related to one another than they are to the mammalian strains. It would appear that the mammalian viruses differ

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sufficiently from one another to be given specific status whereas the avian strains form a much more compact group representing, in all probability, varieties of the same species. Some authorities would divide the avian strains into psittacosis virus, the classical psittacine strains, and ornithosis virus embracing those strains found in non-psittacine birds; it is by no means clear that such a division is justifiable.

Susceptibility of man to these viruses.—There is no really good evidence that the various mammalian viruses are responsible for disease in man. The possibility that the virus of feline pneumonitis might at times infect man has been mentioned but never established. And a strain of virus was isolated from atypical pneumonia in man at Ann Arbor which closely resembled mouse pneumonitis virus in its characters. Recently Giroud and Jadin (1954) have suggested that outbreaks of a febrile exanthem in natives in the Kivu province of the Belgian Congo, which they had shown to be due to a virus of the psittacosis group, might have had their origin in their herds of cattle, sheep and goats with which the natives lived in close proximity. At the time and place of the human outbreaks abortion was occurring in the cows, sheep and goats and Giroud and Jadin obtained some evidence that this disease in the beasts was also due to a psittacosis-like virus; in addition they refer to a case of abortion in a native woman which was possibly due to the same agent. The evidence advanced is insufficient, however, to enable one to adjudge this work so that unequivocal proof of a mammalian virus producing human disease is still awaited. Even though some of them may be pathogenic for man it would not seem that they are highly so since these various mammalian viruses have been worked with quite extensively in the laboratory yet no instances of laboratory infection have been reported. On the other hand the avian strains of virus all seem to be pathogenic for man, some of them highly so. In addition to the infections from psittacine sources, human cases resulting from contact with pigeons, ducks, domestic fowls, turkeys, pheasants, fulmars and canaries are on record.

Relative importance of psittacine and non-psittacine birds as the source of human psittacosis.—The question now arises as to the relative importance of psittacine and non-psittacine birds in the causation of human disease. Quite apart from the scientific interest attaching to this question it has a practical side to it of real importance since the answer might well determine the attitude of a country to the control of the importation of psittacine birds. As psittacosis is not a notifiable disease accurate figures concerning its incidence are not available, but the figures in Table I, which have been extracted from a recent paper by

TABLE I.—INCIDENCE OF HUMAN PSITTACOSIS FROM 1931–1950

	Species of bird											
	Psittacine		Canaries		Pigeons		Ducks		Chickens		Fulmars	
	C	D	C	D	C	D	C	D	C	D	C	D
United States ..	384	43	12	1	136	7	17	0	10	1	—	—
Argentina ..	103	32	—	—	9	5	—	—	4	1	—	—
Faroe Islands ..	—	—	—	—	—	—	—	—	—	—	186	38
Iceland.. ..	—	—	—	—	—	—	—	—	—	—	5	0
France.. ..	9	1	—	—	23	0	—	—	—	—	—	—
Germany ..	447	48	—	—	—	—	—	—	—	—	—	—
Holland ..	48	3	1	0	2	0	—	—	—	—	—	—
Switzerland ..	3	1	—	—	5	0	—	—	—	—	—	—
Total	994	128	13	1	175	12	17	0	14	2	191	38
Mortality per cent	12·9		7·7		6·9		0		14·3		19·9	
					6·8							

C = Cases. D = Deaths

Meyer (1952), reflect the relative importance of these two sources of human infection. It is clear that psittacine birds are the more important. Two other points of interest emerge from a consideration of these figures. One concerns the difference in mortality rates between cases of psittacine origin and those contracted from non-psittacine birds. It is commonly held that human infections coming from non-psittacine sources (ornithosis) run a milder course and have a lower mortality than those of parrot origin (psittacosis) and if one excludes from consideration the cases of fulmar origin, the figures in Table I give some support to this belief. The other feature of interest is this quite extraordinary difference between the mortality rate in the fulmar cases and that for the remainder of the cases of non-psittacine origin, in fact the cases derived from fulmars show a higher mortality rate even than those contracted from parrots and other psittacine birds. As an explanation of this it has been suggested that the fulmars on the Faroe Islands were

in fact, infected with a psittacine strain of virus which had been recently acquired. There are several things which support this suggestion. The severe atypical pneumonia affecting the middle-aged Faroese women in late summer and early autumn had not been observed apparently before the 1930 pandemic and yet the islanders had for long used the fulmar fledglings as winter food. And the fulmar colony on the Faroe Islands is one of the youngest, having been established early in the nineteenth century, yet in the much more ancient colony on the Shetland Islands from which the Faroes were colonized, Miles and Shrivastav (1951) found no evidence of infection with a psittacosis virus. They therefore support the hypothesis put forward by Rasmussen that fulmar infection in the Faroes was contracted by feeding on dead parrots thrown overboard from ships bringing consignments of these birds to Britain and Western Europe in 1929 and 1930.

Mode of spread of infection from bird to bird.—Despite the lack of precise information on this question it would seem clear that the young bird is infected while in the nest. Since there is no evidence that these psittacosis viruses can be transmitted via the egg, this infection must come from contact with the parent birds and although this may result in disease or even death of the young bird, in the majority the infection is silent. A carrier state is set up, the virus being excreted intermittently in the droppings. It is rare in nature for infection in adult birds to become overt but adverse conditions may so disturb the balance between host and parasite as to enable the latter to gain the upper hand. This may even result in extensive epizootics and quite devastating examples of this have been reported in wild psittacine birds both from Australia (Burnet, 1935, 1939) and from the Argentine (Parodi and Silvetti, 1946). The same thing occurs when wild parrots or parrakeets are caught and transported for sale, the adverse conditions of captivity and particularly of the journey to the overseas markets resulting in active disease in the birds which often terminates fatally. It frequently happens, therefore, that consignments of parrots or parrakeets, though in apparent good health when despatched, arrive at their destination with many of the birds dead or dying. These acutely ill birds excrete vastly more virus in their droppings than do the healthy carriers.

From bird to man.—In the very large majority of cases infection passes from bird to man through the air. This is apparent not only from the fact that in human psittacosis the respiratory system bears the brunt of the disease particularly in its early stages, but also from the many examples of persons contracting psittacosis merely from going into rooms in which a sick bird had been housed. The infection can be passed by contact and there are well-authenticated cases where it has resulted from a parrot bite sustained in mouth-to-bill feeding. But the usual route of infection is aerial, the infective material being supplied by the dried droppings.

Control of human psittacosis.—At the time of the pandemic, when psittacine birds were thought to be the sole reservoir of the virus, it seemed logical as a safeguard to man in countries where birds of the parrot family were not indigenous, to control the importation of these birds by imposing an embargo on the practice or by some system of quarantine and inspection. The former method seemed the more likely to be effective and was adopted by this and other countries. When it was realized that many non-psittacine birds were naturally susceptible and that, in fact, reservoirs of infection already existed in countries throughout the world, the argument in favour of a ban on the importation of parrots and parrakeets seemed untenable. As a consequence the embargo was lifted in this and some other countries. This action overlooked certain important facts, not the least of which was that the history of human psittacosis clearly showed that all the serious outbreaks of this disease in man had their origin in recently imported birds of the parrot family. Furthermore, these birds are kept in much closer association with man than those non-psittacine birds which are hosts of the virus, and they are more commonly the subject of acute disease and therefore excreting more virus than the latter birds in which infection is usually present in the form of the healthy carrier state. Lastly there is the very strong suggestion that the strains of virus of psittacine origin are much more virulent for man than those coming from other species of birds. The ban on the importation of psittacine birds was lifted by this country in January 1952, and within two months many outbreaks originating in imported parrots had occurred; between its imposition in 1930 and its lifting twenty-two years later cases of human psittacosis had been few and sporadic. New Zealand, a country in which human psittacosis had never been observed, had imposed a ban on the importation of these birds in common with us in 1930. Moved by the same arguments as the authorities in this country, she removed this ban in April 1952; the first human cases of the disease to be seen in New Zealand occurred between October 1952 and April 1954 (Jeffery, 1954). In both countries the ban has been reimposed. New York State, which had a ban on the introduction of psittacine birds having been free of human psitticosis for the ten years ending January 1952, lifted the ban on that date; two outbreaks, amounting to six cases in all, occurred in May

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1952 (Drachman, 1953). These examples suffice to show that prohibition of the importation of psittacine birds provides a very considerable degree of protection to man against this disease.

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Dr. A. Buxton:

Salmonellosis

Salmonella have been isolated from practically all animal species which have been examined. A discussion on the public health importance of these bacteria in domestic pets, therefore, should take into account all species of animals which might be kept in the home, backyard or garden. Animals kept under these conditions are frequently handled, especially by children, who are more susceptible than adults to infection with salmonella.

Dogs and cats constitute the majority of domestic pets in this country. Other animal species which have close contact with the human population in the home include mice, rats, rabbits, guinea-pigs, hamsters, hedgehogs, tortoises and various species of birds, particularly pigeons, budgerigars, canaries and parrots. All these are susceptible to infection with the genus salmonella, and the type of disease resulting may vary from the symptomless fæcal excreter to the animal which suffers from a severe and often fatal generalized infection. Owing to the limited data available concerning the incidence and pathogenesis of salmonella in some of these animal species, a detailed consideration of this subject must be limited to a few species only, while only brief reference can be made to the possible public health significance of salmonellosis in other species.

Dogs.—Incidence: The bulk of information about the incidence of salmonella in dogs has been obtained only during the last decade or so, and is sufficient to show the importance of dogs as carriers of salmonella and potential sources of infection for man. The wide variation in the incidence of salmonella in the fæces of clinically normal dogs, as shown by different surveys, emphasizes the importance of relating these results to the conditions under which dogs may be kept.

Table I shows the incidence of salmonella in the fæces of domestic and kennel dogs. The term "domestic dog" refers to those animals which, at the time of examination, were living in domestic premises or which had been kept in kennels for only a few days under conditions where it may be considered that the survey result reflected the incidence of salmonella in the dogs during their domestic lives (Cruickshank and Smith, 1949; Adler *et al.*, 1951). In contrast, "kennel dogs" refer to those animals which had been kept under communal conditions of feeding and contact which would predispose to an increase in infection in groups of animals. Table I shows that the incidence of salmonella in fæces from domestic dogs varied from 1·0% in the London area (Cruickshank and Smith, 1949) to an average of 15% in Florida, U.S.A. (Mackel *et al.*, 1952). Moreover, the incidence from clinics in different parts of the State of Florida varied from 1·9% to as high as 41·0% in the region of Homossassa. In non-urban areas around Pullman, Washington, Gorham and Garr[illegible] (1951) found an incidence of approximately 1·0% only in canine fæces. Varela *et al.* (195[illegible]) found an incidence of 9% in Mexico City. In contrast, the occurrence of salmonella [illegible]

the fæces of kennel dogs was, with one exception, uniformly higher than domestic dogs, showing an incidence of approximately 18 to 36%.

TABLE I.—SHOWING THE INCIDENCE OF SALMONELLA IN THE FÆCES OF DOGS AND CATS

Number of fæcal samples examined	Percentage infection	References
Domestic dogs		
1,156	3·4	Watt and DeCapito (1950)
500	1·0	Cruickshank and Smith (1949)
294	13·2	Adler *et al.* (1951)
809	1·2	Gorham and Garner (1951)
100	9·0	Varela *et al.* (1951)
1,626	15·0 (1·9–41·0)	Mackel *et al.* (1952)
Kennel dogs		
100	18·0	Wolff *et al.* (1948)
71	18·5	Kintner (1949)
300	5·6	Ball (1951)
2,548	36·5	Stucker *et al.* (1952)
3,459	17·9	McElrath *et al.* (1952)
Cats		
500	1·4	Cruickshank and Smith (1949)
91	0	Gorham and Garner (1951)
200	2	Ball (1951)

Predisposing factors.—Detailed surveys have resulted in the isolation of more than 40 different salmonella serotypes from dogs kept in different areas and maintained under various conditions. Thus, among symptomless excreters in the U.S.A., a wide variety of serotypes have been identified, and not infrequently two or more serotypes have been isolated from the fæces of a single animal. In contrast, results from the London area have yielded only a few serotypes, of which *Salm. typhi murium* was one of the most frequent. The possible reasons affecting fluctuations in the incidence and number of serotypes of salmonella in the fæces of dogs have been the subject of much recent discussion. It has been noticed that an increased incidence of salmonella infection may be present among dogs suffering from virus diseases such as canine distemper or hard pad disease (Wolff *et al.*, 1948; Kintner, 1949). Although similar relationships between salmonella and intercurrent diseases have been recognized in other animals, Smith and Buxton (1950) did not find a noticeably higher incidence among dogs in the London area suffering from canine distemper or hard pad disease as compared with those which were not suffering from these virus diseases. The relatively high incidence of salmonella in dogs in the U.S.A. may result largely from the feeding of infected foodstuffs (Kintner, 1949; Wolff *et al.*, 1948; Galton *et al.*, 1952). Although this may not be the sole cause, the feeding of dried egg preparations (Wolff *et al.*, 1948) and the presence of salmonella in a high percentage of various dog foods which have been examined by different workers would indicate that infected foodstuffs constitute an important factor predisposing to a high incidence of salmonella in dogs.

Cats.—The incidence of salmonella in the fæces of cats has not been the subject of so much investigation as in dogs. In the London area, Cruickshank and Smith (1949) found an incidence of 1·4%, while in a non-urban area of the U.S.A. Gorham and Garner (1951) failed to isolate a salmonella from the fæces of approximately 90 cats. Around Los Angeles and Honolulu, Ball (1951) isolated salmonella from the fæces of 4 out of 200 cats. In contrast, Mackel *et al.* (1952) examined cats which were in contact with known infected dogs and found an incidence of 12·1% infection in the fæces. Thus, from these limited observations alone, it is clear that, as in dogs, the incidence of salmonella infections among cats may be subject to wide variations, depending upon the conditions under which these animals live. Infected foodstuffs, including wild mice, meat and eggs may be some of the more common sources of infection.

Pigeons.—For many years it has been known that salmonella, particularly *Salm. typhi murium*, causes diseases among pigeons. It is a common practice to keep these birds in lofts situated in the garden or backyard, where they come into close contact with members of the family who look after them. Among adult pigeons, the symptomless fæcal excreter of *Salm. typhi murium* is not uncommon. Cruickshank and Smith (1949) found an incidence of 2·25% in the fæces of pigeons in London. The incidence among groups of pigeons in different lofts may vary. While in some it may be low or even absent, in others the incidence may be extremely high, especially among those birds which have recently survived an outbreak of disease. There exists a potential risk of human infection from dust and fæces

contaminated with salmonella in addition to the risks from the consumption of pigeon eggs and meat which may be similarly infected.

Other animal species.—A variety of other animal species may be kept as pets in the house or garden. It is known that many of these, including mice, rats, rabbits, hamsters, guinea-pigs and ornamental birds, are susceptible to infection with salmonella. Reports of such diseases usually concern colonies of animals among which an epidemic has produced clinical symptoms and a variable mortality rate. However, the incidence of salmonella among those animals which are kept singly or in pairs as domestic pets is unknown. It should be remembered that the introduction of infection to these domestic pets, either from contaminated food or from contact with infected wild mice or rats, may lead not only to a clinically recognizable form of the disease but also to the symptomless fæcal excreter. Tortoises are also known to be carriers of salmonella (Boycott *et al.*, 1953) and to excrete the organisms in the fæces. Such animals may remain symptomless excreters for many months and, therefore, a potential danger to those who handle them. Nevertheless many tortoises, which have been imported from the Mediterranean shores, do not survive for long periods in this country. In addition, it is noticeable that the majority of salmonella serotypes isolated from tortoises are exotic and have seldom or never been isolated from the human population in this country.

Public health significance.—It is impossible to estimate accurately the risk of human infection with salmonella from contact with diseased domestic pets. Many factors which affect this risk are variable and depend to a large extent on local and domestic conditions. The incidence and severity of infection among animals are clearly important features affecting the chances of salmonella becoming transferred to those who handle animals. Cases of human infection undoubtedly arising from the handling of diseased animals of different species are recorded in the literature, and although these are few in number, they do not necessarily reflect the extent to which human infections from these sources may occur. It is difficult and often impossible to obtain suitable material from man and animals for bacteriological examination at the appropriate time. There is little doubt that many cases of salmonellosis in both man and domestic pets remain undiagnosed. Moreover, in some cases of human disease, the tracing of possible sources of human infection, including various foods and human contacts, is time-consuming. When all else has failed, the ultimate examination of an originally unsuspected domestic pet may yield negative bacteriological results or serological reactions which only suggest that the animal may have been the original source of infection. Many owners of domestic pets are unaware that they can contract salmonella infection from these animals, and do not appreciate the risk to themselves from tending animals which show clinical symptoms of infection. When attempting to trace an obscure origin of salmonella infection in a family, therefore, domestic pets should not be overlooked as possible sources. It should also be remembered that pets can contract salmonellosis from members of the household who may be themselves infected; so that in cases of mixed human and animal infections, care must be taken in deciding the primary source of infection within the household.

Conclusion.—There is a potential danger of people becoming infected with salmonella from their diseased pets. Nevertheless, with the limited knowledge available at the present time on this aspect of the epidemiology of salmonellosis, it would be unwise to over-emphasize this possible hazard to human health. Whatever the danger may be, it can be reduced by paying careful attention to personal hygiene and by ensuring that foodstuffs fed to domestic pets are free from salmonella infections.

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Mr. G. C. Brander:

Parasites and Fungi of Domestic Pets (Précis)

There are two aspects to be considered when assessing the importance of the parasites and fungi of domestic animals:

(*a*) The effect of the disease on the animal both for the discomfort caused and the possible disfiguration resulting from skin damage;

(*b*) The danger of transmission from animal to man, especially children.

The development and use of such insecticides as B.H.C. (gammexane) and D.D.T. has reduced the incidence of fleas, lice and mange, although the incidence of infestation on animals is still far higher than is necessary.

As far as fungi are concerned much work is being done, and the setting up of a section at Weybridge to study the incidence of fungi in domestic animals is a step forward. The medical profession, too, is aware of the incidence of fungi on farm workers and liaison between the two professions should lead to active measures being taken to control the spread from animal to man. New fungicides are being developed, but their application is often faulty so that the fresh lesions are often left untreated and the preparation applied to the healed lesion.

Immunity to parasitism is associated with age, and although the mechanism is not completely understood, experiments have shown that young animals do not seem to be able to produce antibodies or phagocytic cells in response to a parasite attack as rapidly as do adult animals.

A state of premunition often exists in host-parasite reactions and the parasite becomes active again only when the host's resistance is lowered.

A feature of both ecto-and endo-parasitism is host specificity.

The main effects produced by the bite of a parasite are redness and swelling of the skin with varying degrees of itching and pain, which result in continual restlessness.

The effects vary according to the parasite, but most blood-suckers act by the injection of an anticoagulant. The reaction of the body to arthropod bites appears mainly to be allergic, and it varies from animal to animal. It is possible, for instance, for lice and ticks to produce such reactions as urticaria, fever, body aches, &c., and it seems probable, therefore, that the unthriftiness seen in animals heavily infested with parasites may not be due entirely to loss of blood and local irritation.

Mr. Brander then described the life cycle of the parasites, the symptoms and treatment of sarcoptic, psoroptic, notoedric and demodectic mange in the smaller domestic animals. Benzene hexachloride is the most useful of the modern insecticides; two treatments at an interval of ten to fourteen days are necessary. Lice have marked host specificity but dog lice which are hosts of the cystic stage of the tapeworm, *Dipylidium caninum*, may pass from the dog to children. Fleas are not so definitely host specific and not infrequently attack abnormal hosts. Since part of the life-cycle is passed off the host eradication requires, in addition to treatment of the infected animal, attention to the house and sleeping place; the most useful insecticides for this purpose are derris and benzene hexachloride. Bed bugs feed on rabbits, mice and rats as well as on man.

The types of ringworm caused by fungi belonging to the genera microsporon and trichophyton were described and their diagnosis and treatment discussed.

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Section of Odontology

President—C. BOWDLER HENRY, M.R.C.S., L.R.C.P., F.D.S. R.C.S.

[*January* 24, 1955]

Continued from May (1955) Proceedings, 48, 409

A Histopathological Study of the Bacterial Plaque in Relation to the Destruction of Enamel, Dentine and Bone with Special Reference to Dental Caries [*Condensed*]

By J. J. HODSON, Ph.D., B.D.S., L.D.S. R.C.S.

Department of Oral Pathology, The University, Sheffield.

STUDIES have been made of the histopathology of the caries lesion in normal, hypocalcified and hypoplastic teeth, particularly in the early stages. In this paper an attempt is made to re-orientate the interpretation of these stages with special reference to the bacterial invasion phase of caries. With regard to the initial demineralization phase, I think we can, within the limits of the microscope, almost prove it to be of environmental origin. It is proposed to refer briefly to some observations on the bacterial plaque and to outline certain histological appearances of the destruction of the enamel, dentine and cementum and to present some correlations between these appearances and those in two cases in which bacterial penetration of enamel in one case, and enamel, dentine and bone in the other, occurred under conditions different from those usually associated with dental caries.

Human teeth only have been used. The various methods of preparation including the decalcification techniques used for the recovery of the organic matrix of both normal and hypocalcified enamel are, with certain modifications, those described in a previous publication (Hodson, 1952).

The plaque.—Observations on the bacterial plaque on enamel and exposed cementum were described. It was noted that the plaque flora showed a rather constant type of organism which morphologically is a Gram-positive beaded or coccoid rod or filament according to size, resembling the lactobacillus (Hadley *et al.*, 1930; Morris, 1953). Coccal or streptococcal bacteria were also common. No morphological feature distinguishes the plaque of the early caries lesion. It is important not to confuse V-shaped developmental defects infested with bacteria, with areas of invasion (Fig. 2B) (Hodson, 1953*d*). The concept of a healthy secondary cuticle on exposed tooth surfaces is deemed fallacious. From the material studied, it was concluded that the keratinized, so-called secondary, cuticle offers no material protection against caries, either in the initial decalcification stages or the subsequent stages of bacterial penetration.

The enamel.—The following is a brief résumé of the main changes in the enamel prior to bacterial penetration. The earliest sign of beginning destruction is a white opacity on the enamel surface, which shows a decrease in calcium concentration, an increased permeability, and a decrease in hardness. The lesion then changes in colour, varying from yellow to brown, apparently due to environmental pigments. These colour changes also affect the enamel matrix, which in bulk appears yellow or brown, and are associated with a resistance to solubility in acid. Depending on the stage and rate of progress, the matrix may also show an apparent increase in organic content and staining properties. *This occurs in caries of both normal and hypocalcified enamel* (Figs. 1 and 2). I have used the term *consolidated matrix*, originally used by Bibby (1932) to describe this appearance (Fig. 1, E, Fig. 2, D). It was first noticed by Malleson (1925) and Bodecker (1927) and in recent years by Hardwick and Manley (1952) and Hodson (1953*a*). Its nature appears to be partly changed enamel keratin and partly additional environmental protein. The area of matrix consolidation does not necessarily coincide with or indicate the extent of the area of demineralization.

This latter process occurs first and, significantly, appears to cause little or no observable change in the matrix, using routine stains. The consolidated matrix is diagnostic of a previously demineralized enamel. Non-consolidated matrix, however, does not necessarily indicate that the enamel prior to histological decalcification was normal.

Examination of undecalcified and histological decalcified sections of the same caries lesion, shows the important fact that the enamel can be demineralized and the process continued for some distance into the dentine, without any bacterial penetration (Figs. 1 and 2). The apparent structural integrity of the matrix in such areas indicates the unlikely occurrence of internal enzymatic degradation of enamel protein to produce sufficient acid to demineralize the area. The microscopical appearances therefore give strong support to the known properties of oral and plaque organisms in producing a demineralizing acid from environmental carbohydrates.

At any time during the demineralization stages a cavity may be produced, or the surface of the considerably weakened enamel fractured or abraded by any of the forces normally present in the mouth.

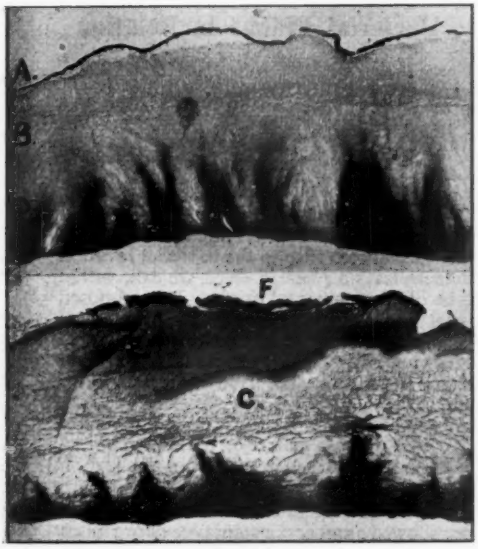

FIG. 1.

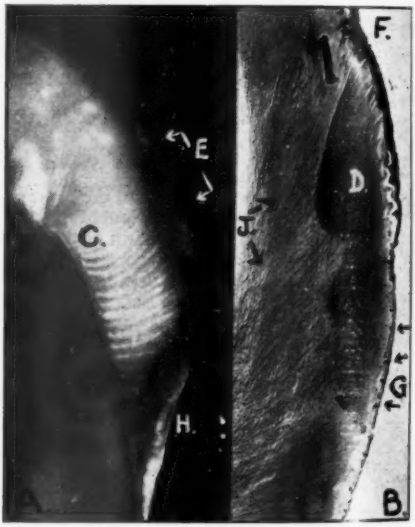

FIG. 2.

FIG. 1.—Decalcified transverse sections of normal proximal surface and opposite brown carious surface of a premolar. Stained Heidenhain's hæmatoxylin. ×62. A=Secondary cuticle. B=Normal enamel matrix. C=Normal-appearing matrix but may be involved in area of carious demineralization process. D=Tufts accentuated by staining. E=Consolidated enamel matrix in area of carious enamel—no bacterial penetration. F=Carious plaque resting on secondary cuticle.

FIG. 2.—A, Bisected surface of a molar with outer thin layer of normal enamel showing caries lesion involving inner hypocalcified enamel (C). ×11. B, Decalcified section from A showing caries consolidation (D) in immature enamel matrix. Stained Mallory. ×63. E=Cone-shaped caries lesion. F=Bacterial plaque—note variation in thickness. G=Bacteria-infested developmental defects. H=Normal enamel. J=Immature enamel matrix.

Bacterial penetration of the enamel.—The absence of bacteria in normal calcified enamel suggests that they do not invade this substance. Bacteria may, however, be found in developmental defects and pre- and post-eruptional cracks. Where bacteria *appear* to invade the enamel substance, it is invariably in a previously demineralized area. Histological sections show that this apparent invasion takes various forms, the picture in any particular specimen depending on the stage, rapidity and location of the caries lesion. In the slow chronic type of caries, as exemplified in the brown proximal lesions showing marked consolidation of the enamel matrix, parts of the plaque appear as though the bacteria were eroding the enamel rods. This is also seen in the enamel of cavity walls (Fig. 3). This apparently always occurs in enamel showing consolidation of the matrix. This appearance of erosion, however, is probably more accurately explained in terms of bacterial alignment

on the ends of fractured rods (cf. Figs. 3 and 18). Islands of matrix seen in surface and cavity bacterial masses almost certainly get there by fracture (Fig. 7). The penetration of bacteria from the cavity or surface plaque described in the literature as inter-rod penetration, is, in my view, via fine fractures between the enamel rods, and not invasion of inter-rod substance (Fig. 7, cf. Fig 17, E). In cross sections of the enamel rods, these bacteria-filled tracts are crescent-shaped and often wider at the site of commencement (Fig. 15). Bacteria are not commonly found within the rods of heavily consolidated enamel matrix.

Partially demineralized enamel is weak, and mastication and other forces, especially on the occlusal surface, often fracture it and dislodge large fragments, with the result that the plaque enters these spaces, and, given the same conditions as were present prior to the dislodgement, a greater area for demineralization is opened up. The observation that *in vitro* acid lesions almost invariably produce fractures, suggests that it is probable that spontaneous fracture, due to the release of intrinsic forces during the cariogenic decalcification, may also occur.

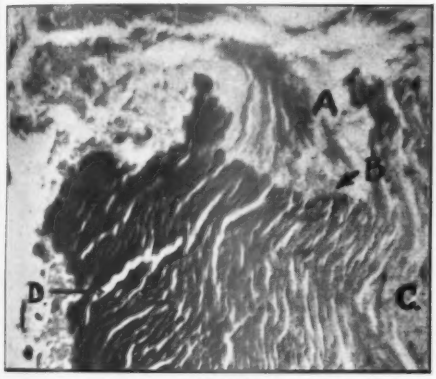

FIG. 3.

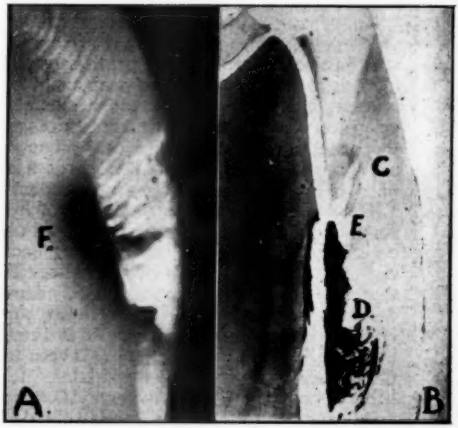

FIG. 4.

FIG. 5.

FIG. 3.—Decalcified section of enamel wall of a carious cavity showing bacterial plaque (A) on fractured rod ends (B). Stained H. and E. ×356. C=Consolidated matrix. D=Histological artefact spaces.

FIG. 4.—A, Bisected surface of white and brown caries lesion on intact proximal surface of a molar. ×13. B, Decalcified section from A showing matrix consolidation (C) and bacterial infestation (D) from lamella (not shown in this section) of internal lightly consolidated matrix (E). Stained H. and E. ×24. F=Staining, shrinkage and lysis of dentine.

FIG. 5.—Higher magnification of serial section of areas C and E from Fig. 4 to show variation in consolidation between outer and inner matrix. Note small plaque. Heavily stained Heidenhain's hæmatoxylin. ×106.

In rapid or acute caries where consolidation of the matrix is much less apparent and presumably has not had time to develop, bacteria are more commonly found within the enamel rods. This suggests that they enter the rods under such conditions more readily. It is interesting that such areas are more frequently found within the body of the enamel, i.e. away from the surface where consolidation changes commence (*see* Figs. 4 and 5). Such bacteria-filled rods tend to be disorganized by mastication and possibly by spontaneous disruption by the caries demineralization process. Where the demineralization has reached to the dentine, the shrinkage which takes place may contribute to the dislocation of the weakened enamel above it. Histological sections of such material, unlike those of heavily

consolidated enamel matrix which is fairly easily decalcified and sectioned, show that bacteria-filled rods are easily disrupted, leaving a somewhat distorted mass of rods and bacteria, a picture conveying the impression of lysis of the matrix. In good longitudinal sections, the outlines of the bacteria-filled rods can be identified. There is, however, little evidence to suggest that the matrix has in fact undergone liquefaction. Fig. 4A shows the cut surface of a white and brown caries lesion with intact outer surface on the proximal surface of a young lower molar. Fig. 4B, a decalcified section from the same specimen, shows an inner bacterial mass and an outer area of consolidated enamel matrix. Serial sections showed that the bacteria entered the internal demineralized area via a lamella. The bacteria have probably entered the "spaces" in the extremely fine rod "reticulum". This latter, as seen in Fig. 5, which needed heavily staining with Heidenhain's hæmatoxylin to show it, is much more lightly consolidated than the surface areas. Since it is difficult to demonstrate this matrix at all, even though somewhat consolidated, the sectional appearance of such matrix, heavily infested by bacteria, is unlikely to show evidence of proteolysis. This may be assumed, but I feel that the appearances are more logically explained in terms of infestation of demineralized enamel matrix.

In normal enamel with developmental or post-eruptional cracks which have been filled with organisms from the plaque, no invasion into rod structure would seem to occur except where these avenues are in a previously demineralized area. No case has been found where the origin of a demineralized area could be attributed to the site of one of these bacterially infested channels. My investigations show that the role of lamellæ in caries is one of extension of cariogenic acids from ætiologically unrelated surrounding lesions which involve the lamellæ, and the infestation by bacteria in the lamellæ, of the demineralized area in advance of the plaque. In other words, a lamella is concerned with the spread and infestation of a caries lesion which arises independently of it.

The question of the susceptibility of hypocalcified enamel to caries has been studied in some detail. It has been demonstrated above that immature enamel in the early phase of caries can be demineralized without bacterial invasion and shows similar consolidation changes to those in caries of normal calcified enamel. *In vitro* studies of acid lesions show that immature enamel is more quickly decalcified than normal enamel and cavitation occurs earlier. It is believed that this more rapid process to which trauma is added occurs *in vivo*. Sections of carious hypocalcified enamel (Figs. 6–9) show a more extensive penetration by bacterial tracts or channels. These latter are without doubt bacteria-infested cracks. Certain exceptions will be noted later. It is of importance to note that these cracks sometimes may extend beyond the area of consolidation of the matrix and, as shown in the superficial cavity in Fig. 8, may reach to the dentine. While I agree with Hardwick and Manley (1952) that most of these cracks occur in previously demineralized enamel, the latter may not necessarily be consolidated.

The origin of bacteria-filled channels is not, however, as simple as would appear, since in certain areas, more especially in immature enamel in groove and hypoplastic lesions, similarly shaped tracts are frequently found in unerupted teeth, and obviously arose during development. Many of these are of crack origin (Hodson, 1953*b*) but where they have become filled with bacteria after eruption, either with or without a surrounding carious lesion, distinction from a post-eruptive crack, or in the former case, a caries crack, may be extremely difficult.

It would appear that bacteria can infiltrate into demineralized enamel (especially via further fractures) from these tracts and set up foci of bacterial masses and disorganized rods. Dense, highly organic enamel rods or parts of rods are, however, not invaded by bacteria. There seems no good evidence that bacteria can infiltrate poorly calcified enamel without previous demineralization. The presence of bacteria in non-carious hypocalcified enamel is found to be in sites of hypoplastic areas and tracts and pre- and post-eruptive cracks. In other words, as stated above, bacteria do not enter the substance of either well-calcified, or poorly calcified enamel. The common occurrence of immature enamel in groove areas, especially in sites with hypoplastic defects, in association with a constant and undisturbed bacterial plaque, may account for the greater rapidity and high incidence of caries in such areas.

In the bacterial penetration phase of caries of the enamel, there is the same predominance of beaded or coccoid rods and coccal and streptococcal forms as is observed in the surface plaque.

Dentine.—Where carious demineralization reaches the amelo-dentinal junction, the most significant feature is the shrinkage of the dentine away from the enamel. It is possible that, as mentioned above, this may assist in the dislocation of the softened enamel above it (Fig. 4). It is also significant that in the early stages of demineralization of the dentine, no apparent structural changes are seen. Invasion of the tubules occurs wherever organisms reach the dentine from outside, pioneering organisms passing apparently down the tubules

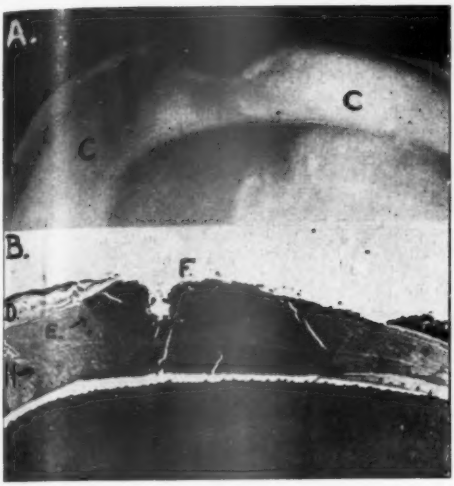

FIG. 6.

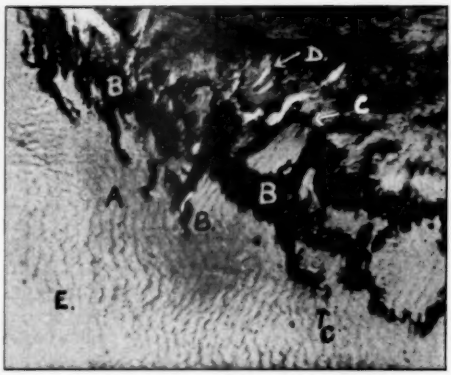

FIG. 7.

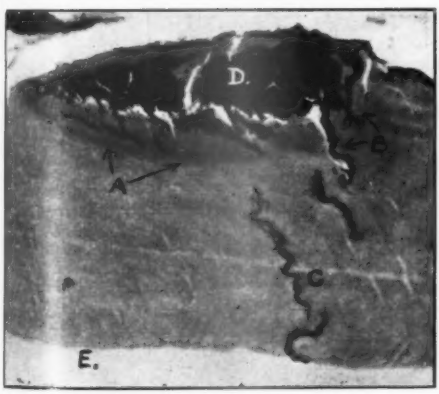

FIG. 8.

FIG. 9.

FIG. 6.—A, Bisected surface of carious cavity involving hypocalcified enamel (C) in a hypoplastic premolar. ×15. B, Decalcified section from A. Stained H. and E. ×30. D=Normal enamel. E=Consolidated matrix. F=Bacterial plaque. G=Dentine. H=Immature matrix corresponding to C.

FIG. 7.—Higher magnification of cavity base shown at E in Fig. 6. No invasion into rods in this field. Stained H. and E. ×253. A=Consolidated matrix. B=Bacteria-filled fracture spaces. C=Fine fracture lines occupied by bacteria (not penetration of inter-rod substance). D=Islands of matrix in cavity debris. E=Non-consolidated matrix.

FIG. 8.—Serial section from Fig. 7 printed darker to show consolidated area (A). Stained Gram-Weigert. ×103. B=Bacteria-filled cracks within consolidated matrix. C=Bacteria-filled fracture extending to dentine out of consolidated area. D=Undermining cavity of disorganized matrix and bacteria. E=Amelo-dentinal junction.

FIG. 9.—Decalcified longitudinal section of cavity wall in a molar with "mottled enamel" (hypocalcified) from S. Shields fluorine endemic area, showing extensive bacteria-filled cracks both parallel to (A) and across (B) the general direction of the rods (cf. non-caries lesion, Fig. 13). Stained Gram-Weigert. ×49. C=Plaque on secondary cuticle. D=Amelo-dentinal junction.

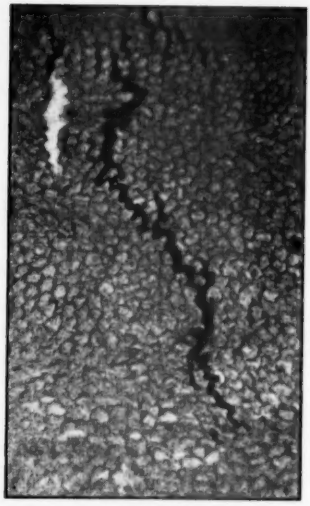

FIG. 10.

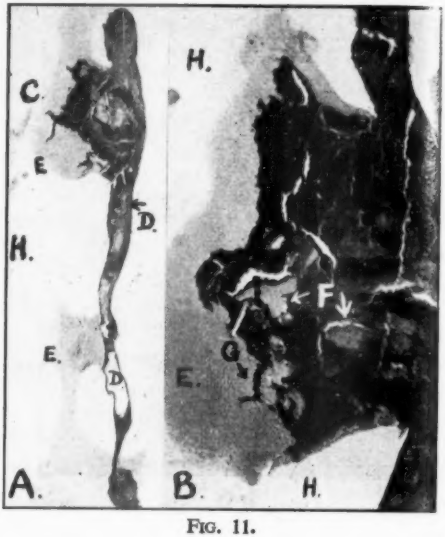

FIG. 11.

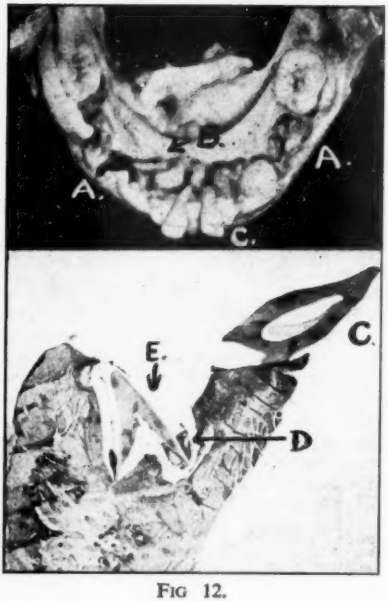

FIG 12.

FIG. 10.—Decalcified section from groove area in unerupted molar showing bacteria-filled crescent-shaped cracks in immature matrix (cf. tracts in caries lesion, Fig. 15B). Stained H. and E. ×660.

FIG. 11.—A, Low power of groove area from unerupted molar showing carious lesion (C) extending into immature enamel matrix from the groove (D). Stained H. and E. ×70. B, High power of serial from C in A. Stained H. and E. ×194. E=Immature matrix. F=Islands of matrix isolated by bacteria-filled cracks (G). H=Acid-soluble matrix.

FIG. 12.—Mandible of jaw from child aged 1 year 11 months with pink disease, and longitudinal section through anterior region. A=Exfoliated teeth. B=Exposed permanent central and lateral incisors. C=Displaced deciduous incisors. D=Immature enamel. E=Hypocalcified enamel, partly acid-soluble.

in the line of the dentinal fibres. In grossly demineralized areas, horizontal and longitudinal cracks in the matrix appear, and these become filled with bacteria and debris. Lysis of the matrix from both cracks and tubules appears to take place and histologically appears more "real" than in the enamel, but this apparently takes place only in the demineralized area. It should be noted that experimentally only dentine has been shown to undergo liquefaction by some oral organisms. The cracks are probably caused by the demineralization process and possibly some trauma.

At the dentinal end of lamellæ in normal teeth, a wedge-shaped area is frequently found, in which are many bacteria. I now believe these to be infested cracks and not wedges of carious dentine. In some cases the appearances are merely those of one or more infected tubules.

Cementum.—Bacteria from the root plaque may be found penetrating the cementum, often parallel to the enclosed fibres. It is possible that the bacteria enter fine splinter lines parallel to the cemental fibres and caused by the caries decalcification. Cementum caries usually appears as a slow disintegration or erosion of the cementum nearest the plaque, the invasion and apparent lysis taking place subsequent to demineralization.

Enamel caries in an "unerupted" molar.—Although no obvious opening into the mouth was observed and no gross pus was present, the finding of a microscopic fragment of vegetable particle in one groove area showed that an opening was or had been present. The tooth was a second lower unerupted molar which was impacted against an unerupted third molar in a male, exact age unknown, but probably between 20 and 30 years.

The second molar showed bacterial invasion of the grooves and some, but not all, of the hypoplastic lesions and lamellæ—only the enamel was investigated. The two predominating types, which varied in distribution in the same and different grooves, were streptococci, often single, and Gram-positive rods with small coccoid bodies, similar to those seen in the plaque and caries lesions in erupted teeth.

In one area containing immature enamel, bacteria were present in the line of the rod cortices, forming arcades (Fig. 10) and simulating infected cracks in enamel caries, especially in consolidated enamel. In this area, however, which was a groove area, these tracts resemble certain tracts between rods arising during development. The appearances here therefore could be those of bacterial infestation of these previously existing tracts. It is noteworthy that the bacteria were limited to these avenues although the surrounding matrix was highly immature. In another groove area, where Gram-positive cocci predominated, bacterial invasion of the immature matrix was found (Fig. 11). Typical, bacteria-filled-crack extensions from the lesion, surrounding and isolating islands of matrix, were also seen (Fig. 11, G).

The pattern of the lesion is clearly that of a carious lesion. The poor Gram-positive staining properties of much of the bacterial mass in the invaded area suggested dead organisms.

The non-invaded part of the immature matrix and an adjacent non-invaded area near the same groove (E in Fig. 11A) stained slightly orange with eosin, whereas the immature matrix in other parts of the specimen stained pink. This suggested that the matrix had undergone some change prior to bacterial invasion. It is possible that this change was an early consolidation change and, if so, it would indicate acid demineralization. No similar changes were observed round the bacterial arcades or lamella in the hypoplastic lesion.

Bacterial invasion of enamel, dentine and bone in a case of oral ulceration in pink disease.—In this case, certain features were observed with regard to the plaque organisms and bacterial invasion pattern in enamel, dentine and bone which throw some light on the histopathological picture of the destruction of the hard tissues in caries, more especially the enamel.

In brief, a male child, aged 1 year 11 months, had been ill for three months, suffering from what was clinically diagnosed as pink disease. He died five days after admittance to hospital, from pulmonary embolism. The child was markedly wasted and had a rash, with peeling of fingers and toes. Teeth were being exfoliated and traumatic ulcerations in the mouth were caused by the child in an effort to allay the irritation. In this way the partly developed mandibular right central and lateral incisors were partly exposed to the mouth (Fig. 12). The enamel appeared intact, hard but white and not fully calcified. The case represents to some extent an *in vivo* experiment showing the effect of exposing bone and partly formed teeth to the action of the mixed oral flora and traumatic forces. Microscopic examination showed some necrosis of gingival tissue, and massive bacterial penetration of soft tissues, dental tissues, including the pulps of the permanent incisors, and bone, including their canals, lacunæ and Howship's resorption lacunæ. Inflammatory cells and areas of necrosis were also present.

In the interpretation of certain aspects of this case, the possible effect on the tissues and oral flora of stagnating food, and the presence of inflammatory exudate and enzymes, must be borne in mind. The permanent tooth germs and some of the bone were dead (as in *in vitro* caries experiments). Trauma by the child was a prominent feature. It should also be noted that in the sections, acid solubility of the enamel does not indicate that calcification was complete (Hodson, 1955).

Organisms in the soft tissues.—There was a striking predominance and almost pure "culture" of two morphological types of Gram-positive organisms—streptococci, single and

in chains, and bacilli ranging from short beaded or coccoid rods to larger or filamentous forms with coccoid bodies. The rods conformed to the descriptions of lactobacillus, given by Hadley *et al.* (1930), but distinction from streptococcal forms was frequently not possible.

The enamel matrix of the partly exposed permanent incisors.—The most striking feature was the presence of bacterial masses or plaques over various areas of the enamel surface (Figs. 13, 14, 17). In some areas, the classical palisading arrangement was present and composed chiefly of coccoid rods. In other areas, single and chained streptococci were also present.

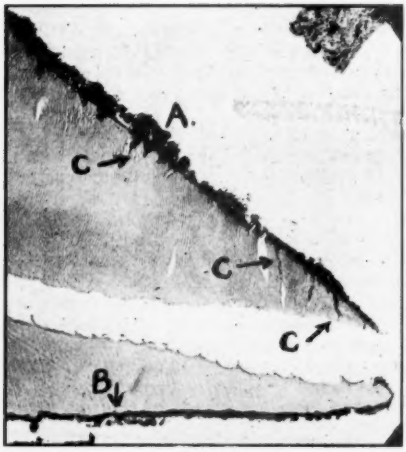

FIG. 13.

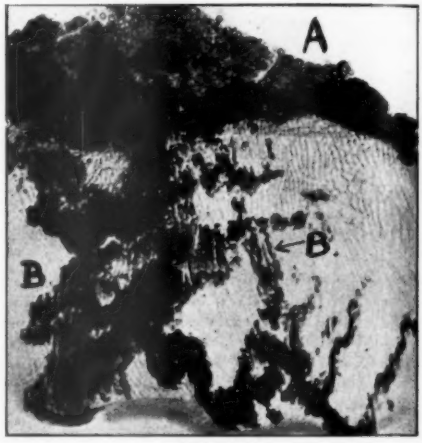

FIG. 14.

FIG. 13.—Section from amelo-cemental area of permanent central germ from case in Fig. 12, showing bacterial plaque on enamel (A) and dentine (B) and bacteria-infested cracks (C) (cf. Fig. 9). Stained Gram-Weigert. ×78.

FIG. 14.—Section of enamel matrix from incisal area of central incisor germ in Fig. 12 showing plaque (A) and illusion of bacteria-filled enamel rods (B) cut longitudinally. Stained Gram-Weigert. ×185.

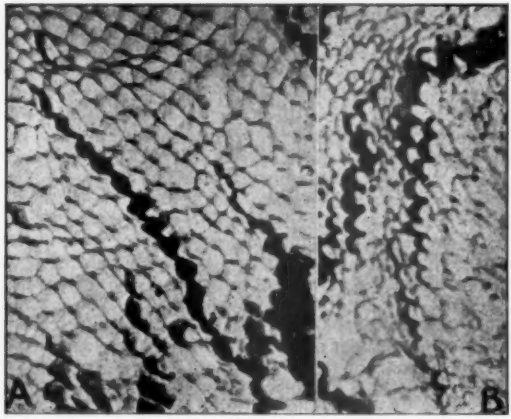

FIG. 15.—A, High magnification of serial from Fig. 14 with cross-cut enamel rods showing bacteria-filled crescent-shaped fine fractures between rods. Stained H. and E. ×578. B. Decalcified section from carious enamel matrix showing similarity of bacteria-filled channels. Stained H. and E. ×923.

The enamel matrix, at various stages of maturity, showed apparent "invasion" by bacteria, mostly in the form of crescent-shaped tracts (Figs. 15A and 17A) when the rods were cut transversely, and an illusion of being within rods, when cut longitudinally (Fig. 14). In the incisal area of the central incisor, the apparent invasion was massive, and here the bacteria had reached the dentine via the tracts, and perhaps by a dislocation of the enamel crown by the child. It was less extensive in the lateral incisor.

One or two long tracts only partly filled with organisms resembled lamellæ. Bacteria were also present in the central area of the enamel tufts which were cut parallel to the dentine.

Except for the tufts and lamellæ, the bacterial penetration, which I believe to be entirely traumatic in origin, so resembled the bacterial invasion phase of caries, that a study of its pattern throws considerable light on this problem. Firstly, the apparent invasion of the enamel rods as seen in longitudinal sections in this case (Fig. 14) is a sectional illusion, and

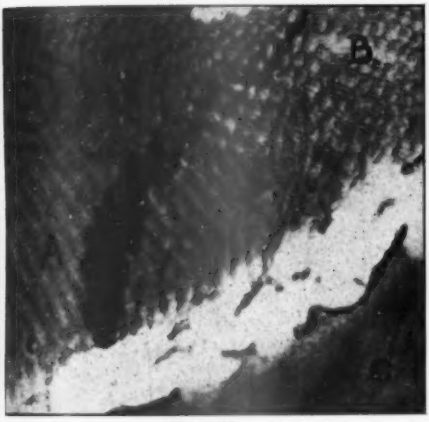

FIG. 16.

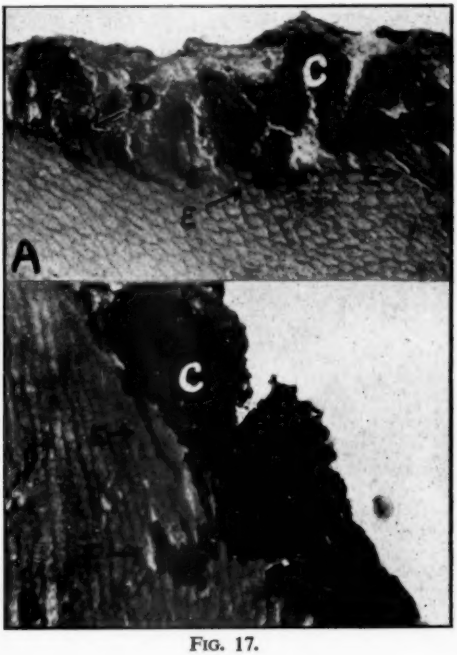

FIG. 17.

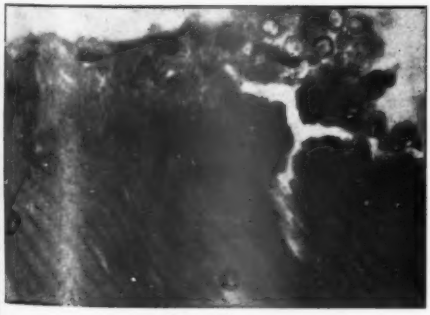

FIG. 18.

FIG. 16.—Section from amelo-cemental area of same specimen as Fig. 15, showing change in appearance of bacteria-filled crack between longitudinally-cut (A) and cross-cut enamel rods (B). Stained Gram-Weigert. ×490. C=Dentine.

FIG. 17.—Sections from amelo-cemental area in central incisor showing fractures and trauma produced spaces filled with bacteria. A, Cross-cut enamel rods. Stained H. and E. ×496. B, Longitudinally-cut rods. Stained Gram-Weigert. ×588. C=Bacterial plaque. D=Isolated islands of matrix. E=Bacteria-filled spaces round dislocated rods. F=Fractured space filled with bacteria.

FIG. 18.—Section of immature enamel matrix showing alignment of plaque (A) on the ends of fractured rods, giving an illusion of bacterial "erosion" (B) (cf. Fig. 3). Stained H. and E. ×674. C=Immature matrix. D=Bacteria in area of dislocated matrix.

the area is actually the appearance in this plane of bacteria-filled cracks between the rods. This illusion in connexion with lamellæ has been described elsewhere (Hodson, 1953c). Although splits across rods do occur, they are more commonly between rods. In a longitudinal histological section, the enamel rods are often superimposed on the bacteria-filled fracture which may not be as thick as the diameter of a rod. Such an appearance may be seen in longitudinal sections of bacterial infestation of demineralized carious enamel and I consider it to be one of the greatest illusions in the histology of enamel caries. This can be quite easily proved by following any bacterial tract from cross cut to longitudinally cut rods (Fig. 16). Frisbie *et al.* (1944), in some of their descriptions and illustrations, have been misled by this appearance. Secondly, whilst the appearance of bacteria in the outer rod cortex or sheath area, especially on one side, as seen in perfect undistorted transverse sections (Fig. 15A), could be interpreted as bacterial penetration in the more organic substance of this area or evidence of bacterial penetration of hypocalcified enamel, careful assessment of the traumatic and other factors present in this case, and close scrutiny of the pattern of the tracts, leaves little doubt that they are due to bacterial penetration of fine fracture lines. Their similarity to the crescent and other shaped tracts filled with bacteria, seen in carious

FIG. 19.

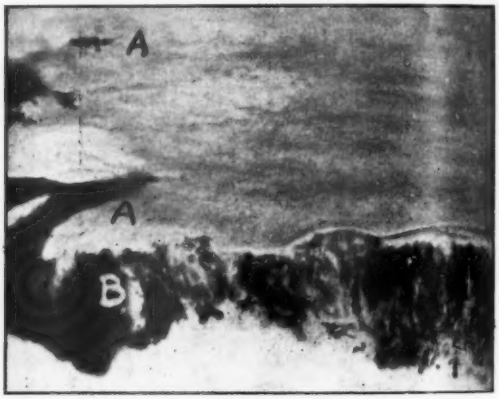

FIG. 20.

FIG. 19.—Showing palisading bacterial plaque on pulpal surface of dentine with infested tubules (A). Stained Gram-Weigert. ×1006.

FIG. 20.—Section of bone showing infested cracks (A) and palisading bacterial plaque (B). Stained Gram-Weigert. ×1080.

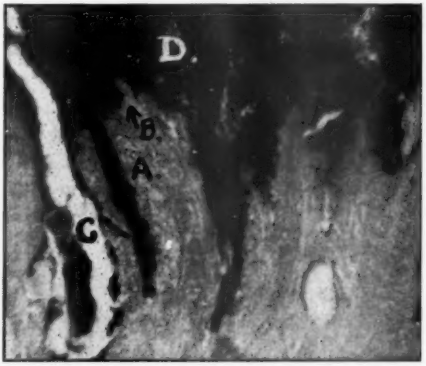

FIG. 21.—Another section showing bacteria-filled cracks (A) fine splinter lines (B) and haversian canals (C) and surface plaque with suggestion of erosion of bone (D). Stained H. and E. ×842.

enamel (Fig. 15B), supports the view that these latter are of similar ætiology and not pioneering organisms entering enamel substance, or tracts produced by lysis of the matrix.

There were also present in the surface areas in this case, islands of matrix separated by bacteria-filled channels, and, in some cases, within bacterial masses. These channels are also of traumatic origin. It is suggested that this offers an explanation of this feature in caries. Fig. 17 shows two areas in the cervical immature enamel cut transversely and longitudinally, in which surface fractures have been filled with bacteria. The larger area F in Fig. 17B is a bacteria-filled space due to dislocation of the enamel rods. In Fig.17A, islands of matrix (D) and individual rods (E) have been dislocated and the surrounding spaces filled with organisms from the surface plaque. In Fig. 13, the thinner enamel towards the amelo-cemental junction has fracture tracts reaching in some cases to the amelo-dentinal junction (cf. caries fracture in Fig. 8). In none of these cases is there any evidence of bacteria within the enamel rods or inter-rod substance.

In some areas of the surface enamel, the ends of the rods were irregular and heavily contaminated with bacteria. When compared with other areas showing fractured rod ends without bacteria, it was clear that they were merely fractured rod ends infested with bacteria and not, as at first supposed, eroded rods as part of a slow proteolytic destruction. Figs. 18 and 3, of infested rod ends in a traumatic lesion and a carious lesion, show a basic similarity strongly suggestive of a common ætiology.

The dentine of the exposed permanent incisors.—The predominant organism in the pulp chamber was the streptococcus, but in some areas a change in the morphology of the organisms was present as the pulpal surface of the dentine was approached. These organisms were morphologically identical with the beaded rods described in connexion with the enamel. At some places on the pulpal surface of the dentine, a quite dramatic picture of an almost pure "culture" of the rods was seen tenaciously attached to the dentine and arranged in striking palisade formation (Fig. 19). The obvious question regarding the bacterial flora here, as well as on the enamel, concerns the possibility that the coccoid rods were related to the streptococci.

Bacteria had invaded large numbers of dentinal tubules, sometimes reaching to the amelo-dentinal surface, but no evidence could be found of lysis of tubule walls. However, there was evidence suggestive of at least a minimal lysis of the dentine matrix in some areas, involving the predentine and dentine at the pulpal end. The apparent lysis in these situations was of the nature of eroded surfaces similar to cervical and root caries in the adult.

While no invasion of intertubular matrix was present in the body of the dentine, in some places organisms had entered interglobular calcification defects from the infested tubules. This might suggest that uncalcified dentine could be invaded and perhaps digested by the bacteria. Elsewhere, areas showed merely infested cracks in the dentine.

Bone.—The two most striking features were the presence in many areas on the surface of the bone of a similar palisading plaque to that previously described (Fig. 20) and apparent extensive penetration by dense bacterial masses (Fig. 21). This, however, was without doubt infestation of fracture spaces.

In some areas the appearances suggested that the bone was being eroded by the bacterial plaque. These sites were comparable to the picture of erosion of cementum in root caries or even dentine. In some areas cocci appeared predominant in the areas of erosion and invasion of bone fracture areas. Here the similarity of wedge and spear-shaped cracks filled with bacteria to those in the dentine at the end of lamellæ, offers further support for the crack origin of the latter. The presence of single lines of coccal bacteria, apparently within the bone matrix, is due to infestation of fine splinter lines and not invasion of bone matrix. It is possible that the so-called invasion by bacteria in cemental caries, is of a similar nature.

An attempt has been made to clarify the interpretation of the histopathological picture of the caries lesion, particularly in the enamel. The appearances observed have been examined in the light of the known properties of the bacterial plaque, the forces continually present in the mouth and the structural characters of the enamel. The apparent structural integrity of the enamel matrix and in the early stages, the dentine matrix, in association with the loss of calcific material and the absence of bacterial penetration, is in full accord with now almost conclusive data showing that dental caries is primarily an acid demineralization of the teeth, due to bacterial degradation of environmental carbohydrates. Regarding the possibility of a dual process, there is no indication that caries may, under certain conditions, or in certain areas, be proteolytic in origin.

In the enamel, evidence has been shown that the bacterial invasive phases are largely in sites of fracture and dislocation of the enamel rods due to trauma and also forces associated

with the demineralization process (e.g. gas, shrinkage, &c.). Support for these views has been found in two cases, one showing infestation of cracks extending from a carious lesion in an infected unerupted tooth, and the other in a case of bacterial infection of exposed developing teeth and bone associated with severe external and occlusal trauma (manual and teeth grinding). The similarity of the enamel lesions in this case to those in the bacterial penetration stages of caries seems to be significant.

The strengthening, as it were, of the fragile enamel matrix by the consolidation process after some demineralization, must be viewed in the light of a somewhat slow process. Bacteria do not seem easily to penetrate demineralized consolidated rods in caries areas. In acute caries with rapid demineralization and spread of bacteria in extensive tracts, the entry of organisms into the open "reticulum" of the rod, and infestation of collapsed and fractured matrix, offers a more likely explanation than lysis of what is known to be a highly resistant keratin.

The widely accepted belief that immature enamel is more susceptible to bacterial penetration and proteolysis, is not supported. Indeed, bacteria do not appear to enter highly immature matrix, but in sites of fractures and developmental defects. The similarity of the consolidation changes to those in normal matrix in the absence of bacterial penetration suggests that, like normal enamel matrix, it is not susceptible to enzymatic hydrolysis. Its more rapid demineralization and consequent susceptibility to dislocation accounts for the evidence that it is more easily destroyed in a caries environment.

ACKNOWLEDGMENTS

Thanks are due to Dr. J. L. Emery for the post-mortem material, to Mr. M. Rudland for his technical assistance, and to the Medical Research Council for some financial assistance.

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Section of Epidemiology and Preventive Medicine

President—Professor A. BRADFORD HILL, C.B.E., D.Sc., Ph.D., F.R.S.

[*March* 25, 1955]

DISCUSSION ON NATIONAL SERVICE MEDICAL EXAMINATIONS AND EPIDEMIOLOGICAL RESEARCH

Dr. J. A. H. Lee (London School of Hygiene and Tropical Medicine):

Some Examples of the Kind of Problem that can be Attacked by a Use of the Findings of National Service Medical Boards

SINCE 1939 a very large number of young men have been called up for military service. Since the end of the war this call-up has been restricted to young men who have either just reached their eighteenth birthday, or who have been engaged in an apprenticeship or in full-time education for a few years beyond this. Further, men in certain occupations are not called-up, provided that they stay in them. Within these limits an almost complete cross-section of young men are medically examined in a detailed and thorough manner. The information derived from these examinations—which are, of course, expensive in money and in medical man-hours—is used for deciding whether or not individual men are fit to serve. It is used for nothing else. No general picture is made of the health of these young men, and hence of the male population of this age, and no studies into the incidence of disease among them are made officially. The statistics that are published are most meagre, and have not increased in scope or adequacy since the days when the entire effort of the country was devoted to the urgent needs of war.

In recent years various people have realized that there might be useful things to be discovered by a study of the findings of these Boards. Dr. Alice Stewart and Dr. Josefine Webb, at Oxford, have been looking at the problem, and so have Dr. E. M. B. Clements in Birmingham, and Dr. M. E. M. Herford in Slough, and there may be many others. I myself have been working in the field for the last two and a half years. All the studies so far made have been independent and small in scale. Although not initiated officially, they have all used facilities provided by the Ministry of Labour and National Service. Something like 200,000 of these medical examinations are made every year. The briefest consideration of this, coupled with the realization that there is almost no element of self-selection about the men examined, shows that there ought to be something interesting in the study of the mass of results obtained.

There are, of course, disadvantages in this method: the situation is peculiar, in that there may be strong emotional associations either with the discovery or the non-discovery of defects; the amount of social information available about the men is limited; there are very many Boards, and there may be substantial variations in their reports of their findings.

My own work has consisted of the study of the documents of just over 7,000 men who were examined in four different areas in Britain: namely in the Home Counties; in North-West London; in South-East Lancashire; and in Clydeside. They were chosen for their diversity, and because the proportion of men rejected varied widely from area to area.

The Services are interested in the intellectual capabilities of the men that they recruit. To sort out their men into the various grades of ability they submit them to intelligence tests, some of which are given at the time of the medical examination. The advantage of this from a purely scientific point of view is that all the men examined are tested, as it is

not known who will be rejected. In Table I are shown the mean scores in the test used

TABLE I.—MEAN TEST SCORES OF MEN IN THE SURVEY WHO OPTED FOR THE ARMY

Home Counties	North-West London	South-East Lancashire	Clydeside
27·6	28·5	27·2	23·4

for men opting for the Army. There are clear differences.[1] I have not applied any tests of significance to these data, but the findings are in broad agreement with those of the much larger samples analysed by the Army Operational Research Group, and they also correspond with those reported by Vernon (1951). I think that there is no doubt that these differences are real; and this poses a variety of problems, both theoretical and practical. A small change in the mean of a Gaussian distribution results in large changes in the proportions of the population above or below any fixed level near the ends of the distribution. Do these alterations in the averages mean that there are quite different proportions of people with very high or very low intelligences in different parts of the country? Should this affect the policies of different Regional Hospital Boards and Local Authorities? More fundamentally—what are these tests measuring that is varying in this way? What proportion of the ability to do these tests is genetically determined, and what socially? It is immediately clear that the areas where the mean score is low are very broadly the areas where the vital statistics have lagged behind those of the more fortunate areas. What are the relations here—is there any degree of direct association between these two variations? Finally, what is the mechanism of the production of these differences? If the differences are of constitutional origin, this pattern looks as if it might have been produced by the known propensity of the intelligent to migrate, although the Clydeside figures are an exception to this. I do not know, and certainly the data can, at the moment, do little more than underline the fact that there are problems. I suggest that this method of study would go some way towards defining them.

There are about 200,000 of these examinations every year, and the great majority include mass miniature radiography. This has the most obvious possibilities for contribution to our knowledge of tuberculosis, but, again, no general picture is made of the data acquired. For instance, there is no picture made of the different proportion of positive cases found in different areas. At this point a clear distinction must be made between men rejected because of healed pulmonary tuberculosis, and men with active and progressive disease. The Services are very conservative in their attitude to men who at any time have had this condition, or who show minimal lesions on radiography. However, the findings, even for the small number that I have been able to look at, are striking enough (Table II). The

TABLE II.—REJECTION RATE PER 1,000 DUE TO ALL FORMS OF TUBERCULOSIS

Home Counties	North-West London	South-East Lancashire	Clydeside
8	11	15	36

change in the rejection rate from the Home Counties to Clydeside is dramatic. This, of course, follows the death-rates. This rate is a true prevalence, and there is some evidence that it follows the death-rate better than does the notification rate. As such it may have some future use as a measure of the extent of tuberculous disease in the community. The principal point that I wish to bring out is given in Table III. This shows the state of the

TABLE III.—THE DIAGNOSIS OF PULMONARY TUBERCULOSIS (NUMBERS OF MEN)

	Men diagnosed before the Board's examination	Men diagnosed by the M.M.R. at the examination
All men rejected because of pulmonary tuberculosis	27	33
Men with definite active pulmonary tuberculosis	16	7

men at the time when they become due for the Board's examination—whether their disease had already been diagnosed or not. As I said, the rejection rate includes anything in the chest that *might* become active during a man's service. However, in the study were included 23 men with unequivocal pulmonary tuberculosis—all of those diagnosed before the Board's examination had received in-patient care for it, and all those found by the mass

[1]The test used is known as the Recruiting Office Test 57, and the maximum score is 56. In this study, for reasons which are not at the moment clear, test scores were not recorded for a small proportion of the men. However, I have based the rest of my comments on the much larger samples of the A.O.R.G. and of Vernon (1951), which do not have this disadvantage.

miniature radiography part of the examination had either cavities or extensive infiltration that was considered to be active.[1] Thus at any one time a very substantial proportion of the men of this age group with active pulmonary tuberculosis have not yet been diagnosed.[2]

If the criteria for the diagnosis are put a little lower than this—for the previously diagnosed, a further 7 may be added who were under the care of chest clinics; and for the newly diagnosed a further 16 who were referred to their own doctors (the Boards do not refer a man for treatment except to his own doctor) or who were kept under supervision by the chest physician who made the radiographic diagnosis. Thus it can be said that somewhere between a half and a third of the men of this age group with pulmonary tuberculosis have not been diagnosed (*see* footnote[2]).

This is based on the findings of a small study, that was not specifically directed towards the problem of tuberculosis. I believe that these findings are sufficiently striking to warrant a further investigation into this point.

Otitis media is a condition that is greatly influenced by adverse social conditions, and its incidence is now much less than formerly. Further, it is responsive to treatment with the chemotherapeutic drugs developed in the last twenty years. However, the method of study does provide a good deal of information about this condition, and raises several puzzles.

First it is one of the most common causes of rejection—in my series it was about 3%. And rejection is not because of mere scarring of the drum, or even because of a single dry perforation. The disease must be active, or bilateral. There is a marked regional variation—nearly as marked as that for tuberculosis. The rates in my four areas of study are given in Table IV. This regional variation is confirmed by the findings of the School Health Service.

TABLE IV.—REJECTION RATES PER HUNDRED DUE TO CHRONIC OTITIS MEDIA

Home Counties	North-West London	South-East Lancashire	Clydeside
2·2	2·6	3·2	5·9

Otitis media is thus still a very common condition among young men; it is also an important condition. The Boards do not employ mechanical aids in the detection of deafness (although consultants to whom they refer may do so) and they found that 47 men had significant degrees of deafness out of the 7,000. In the 47 men, the deafness was due to otitis media in 35. Deafness, to be clinically appreciable, is likely to be of actual importance to the man. In a recent series of brain abscess collected since 1950, out of 36, 14 were due to mastoiditis (Lewin, 1955).

Otitis media has a strong social gradient, becoming much commoner among those less well off. This can be shown in an interesting way. The Boards classify men into those who are of average intelligence—the M2's; those who are rather dull—the M3's; and those who are of too low intelligence for military service—the M8's. (Actual mental defectives are not required to register, but there is a gap between this and the lowest ability that the Services can use.) The association between otitis media and this grading is shown in Table V.

TABLE V.—THE ASSOCIATION BETWEEN THE PREVALENCE OF OTITIS MEDIA AND MENTAL ABILITY

	M2 Average or better	M3 Dull	M8 Much duller
Rejection rate per 100 due to otitis media	2·6	5·2	10·2

The practical point about this is that all chronic otitis must cause some diminution in hearing, and it follows that the incidence of *minor* degrees of deafness among those of low intelligence must be unusually high. I think that we may surmise that degrees of deafness that would have little effect on, for example, a school child of normal intelligence, would have a much greater effect on a child of low mental ability who was only just able to keep up with its class.

There is general agreement that otitis media has become less common. Unfortunately, there are no data about the trend of rejection due to it. The findings of the School Health Service can, however, tell us something (Fig. 1, *see* C.M.O. Ministry of Education, 1940–1954). There has been a fall in the prevalence of cases of the disease needing treatment, but the numbers requiring observation have steadily risen. This looks as if the changes in treatment and its availability are more important than changes in the actual incidence of

[1] Men who are ill or obviously crippled are not generally called for medical examination on the advice of the Chairman of the Board, who will have seen the medical details.

[2] This statement is, of course, based on the numbers of cases that remain to be newly diagnosed by the N.S. Medical Boards.

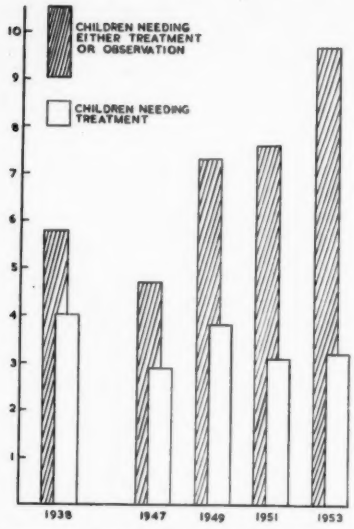

FIG. 1.—Otitis media per 1,000 routine inspections S. H. S.

the condition. There is one difficulty that I should mention. As I have shown, on some occasions data from the School Health Service support the findings of this study of National Service Medical Boards. However, the rejection rate due to otitis media is about 3% in my study. (Unfortunately, as there are no official published statistics, I can produce no fuller confirmation of this.) The prevalence of the condition as found by the School Health Service is approaching 1%. Thus there is a large difference between the two estimates of the prevalence of chronic otitis media, which seems to need explanation. Medical examinations for National Service are usually about three years after the last routine examination of the School Health Service. Further, the National Service figures refer to a narrow age range, whereas the published School Health Service figures refer to the average of all routine inspections over the whole school age. If there is a steep gradient in the incidence of this condition with age, this might explain these differences. If it did, it would be a most interesting finding. Also the School Health Service figures include girls as well as boys and there may be a large sex difference in the prevalence of the condition. Finally, of course, the types of examination are very different. It should be possible to reconcile these two widely differing estimates of the prevalence of this condition, and it might provide a useful contribution to our knowledge of its epidemiology.

These are a few of the things that have come out of this study. I have given them not for their own interest alone, but as examples of the kind of information that can be obtained. It seems to me that such studies would be of use in specific epidemiological problems.

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Dr. Josefine Webb (Social Medicine Unit, Oxford):

In the following communication the value of the clinical data amassed by National Service (Civilian) Medical Boards will be considered from the point of view of epidemiological research. The report is based on 50,000 records and represents the findings of three regions (Leicester, Northampton and Essex) during the period 1941–44, when men from 18–45 years of age were being examined.

VALIDITY TESTS

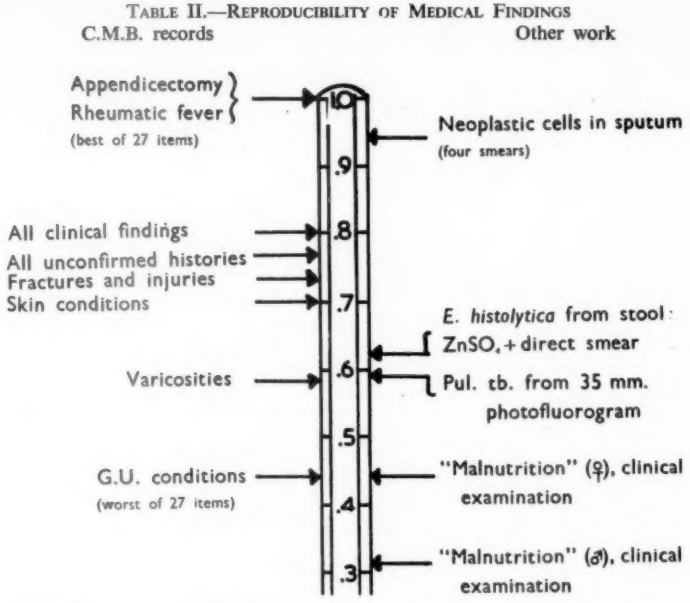
(1) *Re-examination tests.*—The records of 329 men examined by more than one Board were compared in order to assess the element of personal error in the recording of various types of clinical data. For height and weight records the correspondence between paired records was good (Table I) but for entries describing past and present clinical abnormalities

TABLE I.—REPRODUCIBILITY OF MEASUREMENTS

Item	Number of individual pairs of measurements	Mean differences between measurements			
		All pairs	Age in years at first examination		
			18–24	25–34	35+
Height	329	− 0·03	+ 0·10	− 0·04	− 0·12
Weight	329	+ 1·41	+ 2·77	+ 1·31	+ 0·54

it ranged from complete agreement (in the case of appendicitis and rheumatic fever) to less than 50% agreement (in the case of genito-urinary conditions). Nevertheless compared with other studies of "observer error" the results are moderately reassuring (Table II).

TABLE II.—REPRODUCIBILITY OF MEDICAL FINDINGS



(2) *Inter-regional tests.*—Comparison of all entries under clinical findings and medical history revealed consistent wide differences between the three regions which indicated that the standard of recording was highest in Essex and lowest in Northampton. When, however, causes of rejection *only* were compared there was little to choose between the three regions in respect of overall incidence and prevalence of individual diseases (*see* Figs. 1 and 2, also Stewart *et al.*, 1955*a*).

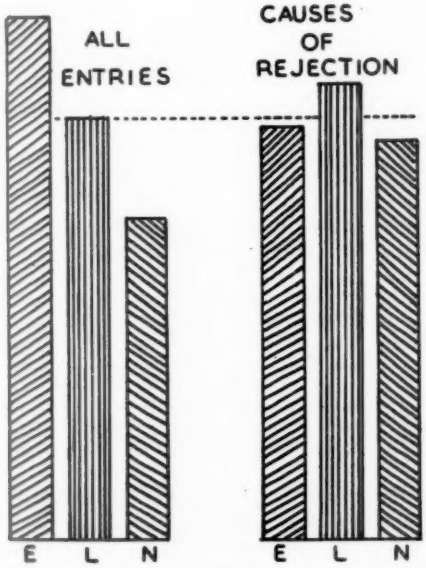


FIG. 1.—All categories of disease, by region. E, Essex; L, Leicester; N, Northampton.

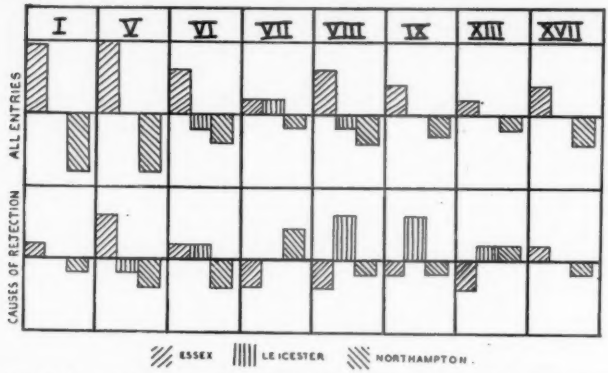


FIG. 2.—Main categories of disease (I.C.D., 1948). I, infective. V, personality defects. VI, C.N.S. and sense organs. VII, circulatory. VIII, respiratory. IX, digestive. XIII, bones and organs of movement. XVII, accidents.

(3) *Occupational comparisons.*—The recording by two Boards (Northampton and Leicester) of the injuries sustained by men in eleven occupational groups is diagrammatically represented in Fig. 3. Each mark (X) on the graph is derived from the two independent

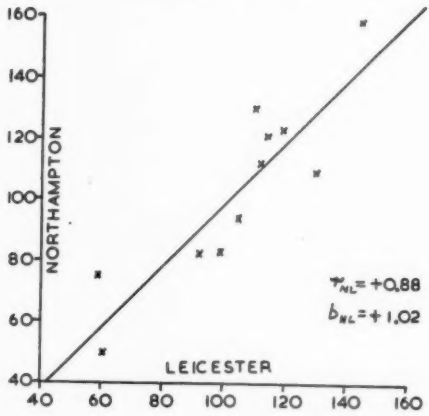


FIG. 3.—Age-standardized prevalence ratios for injury related to occupation. Comparison of two regions.

estimates of "occupational prevalence". Had there been the same occupational prevalence in both regions all the (X) marks would have lain on a straight diagonal line. As it was the linear correlation coefficient was + 0·88, and the regression coefficient (shown on the diagram as the line of best fit) was + 1·02.

The main conclusion to be drawn from these preliminary investigations is that in spite of varying standards of recording, there is for certain items (e.g. weights and heights, serious disabling diseases, and major events in the medical history) fairly close correspondence between the records of different medical Boards.

PHYSICAL AND OCCUPATIONAL CHARACTERISTICS OF CERTAIN DISEASES

Absence of uniformity in the recording of minor disabilities necessitated separate handling of the records of different Boards, but the following results were reproduced in each of the three sets of records examined. They illustrate findings which have been reported elsewhere in greater detail (Hewitt *et al.*, 1953; Webb, 1955; Stewart *et al.*, 1955*b*, *c*).

Varicosities and height (Fig. 4).—The prevalence of varicoceles increased continuously with height to reach, among men measuring 6 feet or more, a level which was three times higher than in the group measuring 5 ft. 2 in. or less. Comparable results were also obtained for varicose veins. It is concluded that a linear relationship between standing height and risk of varicosity exists.

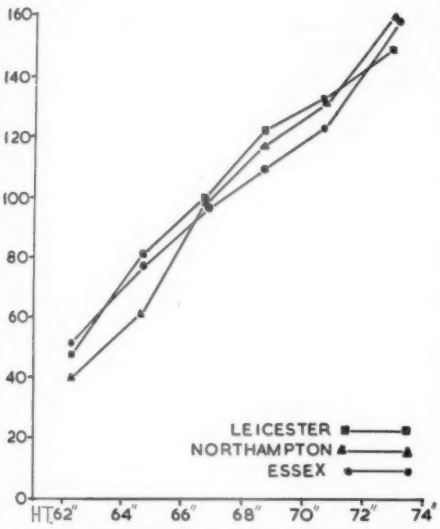


FIG. 4.—Age-standardized prevalence ratios for varicocele related to height (in inches). Three regions separately.

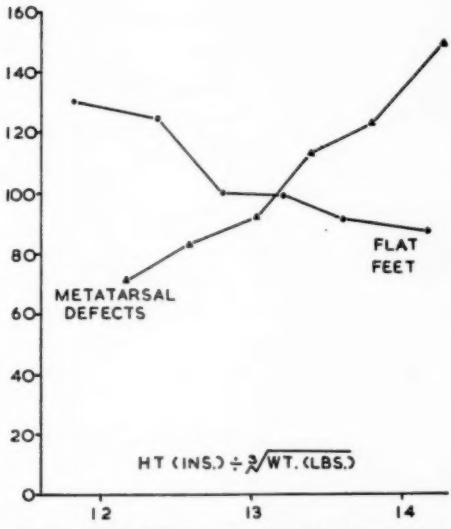


FIG. 5.—Foot defects and body build. Age-standardized prevalence ratios (Leicester only).

Foot defects and body build (Fig. 5).—Men of stocky build developed flat feet more frequently than men of slender build, but the latter appeared to be exceptionally prone to metatarsal defects such as hammer toe, overlapping toes, hallux valgus and hallux rigidus. That is to say overweight appears to predispose towards collapse of the longitudinal arch, while the possessor of a long narrow foot is particularly liable to the ills which follow collapse of the transverse arch of the foot and to toe troubles.

Social distribution of acne in younger and older men (Fig. 6).—An interesting example of

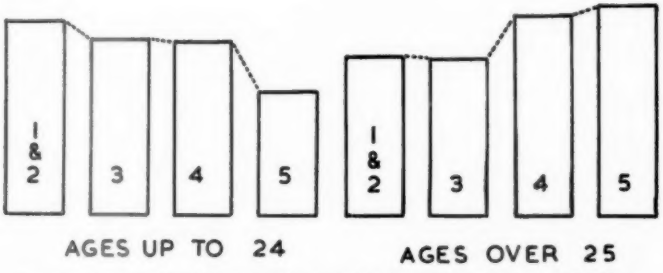


FIG. 6.—Age-standardized prevalence ratios for acne related to social class. Three regions combined.

how the effects of economic status vary with age was found in the case of acneiform eruptions (e.g. acne, chloracne, &c.). In men under 24 years of age these conditions appeared to be a disease of affluence, but at older ages they appeared as a special risk of the unskilled worker.

Physical fitness of professional drivers (Table III).—It is well known to members of the

TABLE III.—CAUSES OF REJECTION OF PROFESSIONAL DRIVERS

Eyes:	
High myopia and pathological conditions	10
Ears:	
Defective hearing and pathological conditions	13
C.N.S.:	
Organic conditions	7
Mental deficiency and instability	10
Skeletal:	
Lower limb conditions	27
Other skeletal	13
Cardiovascular conditions	32
Respiratory conditions	27
Abdominal conditions	30
Other pathological conditions	14
Total number of drivers rejected	183
Total number of drivers examined	1,276
Rejection rate	14%

medical profession that car owners are extremely reluctant to admit that they are no longer fit to drive, but the total numbers of unfit drivers on the roads is unknown. Judging by the present set of records, even among relatively young *professional* drivers the proportion is far from negligible (Table III). Thus among the 1,276 men described as drivers of road vehicles, epilepsy, blackouts, loss of power in the limbs and high myopia all featured in the list of disabilities recorded at the time of call-up.

CONCLUSIONS

In spite of a natural reluctance on the part of the medical profession to regard "routine clinical records" as reliable sources of information, an intensive investigation of Civilian Medical Board records has shown that they have considerable value to students of epidemiology. It is suggested that the value of these and other mass records would be enhanced if it were more widely known that academic departments of social medicine are interested in the design of schedules for routine medical examinations and can make special use of the data collected.

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JOINT MEETING No. 6

Section of Pathology with Section of Epidemiology and Preventive Medicine

Chairman—Professor L. P. GARROD, M.D., F.R.C.P.
(President of the Section of Pathology)

[*March* 1, 1955]

DISCUSSION ON CORONARY ARTERY DISEASE

Professor T. Crawford: *The Morphology of Coronary Atherosclerosis in Man*

Naked-eye appearances of coronary atherosclerosis.—These are the well-known pictures of yellow or whitish patches in the intima varying from minute flecks up to big encircling plaques which may become confluent and calcified to convert segments of the vessel into a rigid pipe stem. The effect of the plaques on the calibre of the vessel is difficult to assess, and it is certainly not true that large plaques necessarily narrow the lumen. The usual post-mortem room technique of opening the arteries with scissors gives only a rough idea of the state of the lumen in life, and I believe that for an accurate assessment an injection-X-ray technique is necessary.

Normal histology of coronary arteries.—The normal coronary artery has a considerably thicker intima than other arteries and even at the age of 10 the intima is about the same thickness as the media.

Early lesions.—Sections through lesions just visible to the naked eye show thickening and œdema of the intima and the presence of a small amount of Sudan-staining fat. This may be diffusely scattered through the intima or it may be collected into the cytoplasm of histiocytes which form an aggregation just below the endothelium.

Advanced lesions.—As one examines progressively more advanced lesions one finds that the collection of fatty material comes to be separated from the lumen by a laminated layer of rather acellular collagen. The collection of fat-laden cells often breaks down to give an extensive area of amorphous debris rich in fat and cholesterol crystals. The vessel now has a well-marked "signet-ring" deformity, though this is less evident if it is fixed in the distended condition (Crawford and Levene, 1953). There is little or no relationship between *number* and *severity* of plaques. In younger subjects dying from coronary lesions one often finds that occlusion has occurred at one of a very few plaques present: whereas in elderly people there are often very numerous severe lesions without thrombosis.

Subsequent course.—If the subject survives after complete occlusion of a vessel the subsequent structural changes may take one of two courses:

(*a*) A new lumen may develop quite quickly by retraction of the thrombus, the thrombus becoming separated from one side of the vessel. Organization converts the retracted thrombus into an eccentric thickening of the intima, and the net result is simply an increase in thickness of the original plaque at which the thrombosis developed.

(*b*) If the thrombus fails to separate from one side of the vessel as it retracts, then no main lumen will be re-established, but, instead, several small channels will develop. These result from fusion of the capillaries which extend into the thrombus during the process of organization and sometimes they are so numerous as to amount almost to cavernous transformation of a segment of the vessel. These new channels seem often to be of only temporary value to the circulation, for one often finds evidence of the thrombotic process being repeated in them.

The thrombogenic theory of atherosclerosis.—Perhaps the most important recent contribution on the morphological side to the study of the pathogenesis of atherosclerosis has been Duguid's demonstration (1946, 1948) of the part played by mural thrombosis in the development of the atheromatous plaque. This work is now so well known as to require only the briefest reference here. Duguid and some subsequent workers have shown that fibrinous encrustations of varying size and thickness are frequently being deposited on the intimal surface, and that they quickly become covered by a layer of endothelium and then become organized by a dual mechanism both from the surface and from the vasa vasorum in the media (Crawford and Levene, 1952). Small encrustations thus lead to nothing more than

some fibrous thickening of the intima; but larger mural thrombi, or repeated deposits at the same site, may result in a mural plaque in which organization is incomplete. When that happens the central parts of the plaque come to consist of amorphous debris rich in lipoids and separated from the lumen by laminated hyaline collagen strands—appearances indistinguishable from the classical atheromatous plaque.

Conclusion.—Even the most ardent supporters of this thrombogenic hypothesis cannot maintain that mural thrombosis and the subsequent modified organization process are more than a stage in the development of the full lesion. The hypothesis leaves unexplained the causation of the encrustations and larger mural thrombi, and also their patchy distribution and localization.

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Dr. J. E. French: *Atherosclerosis in Experimental Animals*

It is only in man that atherosclerosis occurs at all commonly as a spontaneous disease. Lesions of the intima of major arteries, resembling the lesions of atheroma in man, have been produced, however, in experimental animals by a number of artificial procedures. As a generalization, it can be said that nearly all the significant observations have been made in animals in which there is some gross disturbance of the normal lipoid metabolism.

The lesions in animals which have been studied most are those occurring in rabbits or chicks fed a gross excess of cholesterol in the diet (Anitschkow, 1913; Dauber and Katz, 1942), or in dogs in which cholesterol feeding is combined with impairment of thyroid function, usually by thiouracil administration (Steiner and Kendall, 1946). An interesting recent development is the production of lesions in Cebus monkeys which have been given a diet deficient in methionine and then fed an excess of cholesterol (Mann *et al.*, 1953). Rats appear to be particularly resistant to the effects of cholesterol feeding, but it has been claimed that lesions may be produced in these animals by a rather rigorous combination of factors (Wissler *et al.*, 1954). Mention may also be made of the lipoid accumulation which occurs in the major arteries of rats on a diet deficient in choline but without added cholesterol (Wilgram *et al.*, 1954). The morphology of the lesions in these animals, however, differs from that in the other types of experiment and it is probably advisable at present to consider them as belonging to a separate category.

With this exception, the lesions in experimental atheroma have a fairly uniform appearance and consist essentially of accumulations of lipoid material, mostly within macrophages or "foam cells", lying immediately beneath the endothelium of the aorta or other vessels. Chemical analysis of such lesions shows a marked excess of free and total cholesterol as well as a significant, though variable, increase in the phospholipoids and triglycerides (Weinhouse and Hirsch, 1940).

It has been argued that the lesions produced in the experimental animals differ in various respects from the fully developed lesions of atherosclerosis in man. It can be generally agreed, however, that the two types of lesion have in common the accumulation of lipoid material in the arterial intima, and that the chemical composition of this lipoid suggests an origin from the plasma lipoids (Hirsch and Weinhouse, 1943). If these two propositions are accepted it seems that animal experiments should provide significant information on the factors which determine transfer of lipoids from plasma to the arterial intima. This does not, of course, imply that, in man, no other factors contribute to the diverse manifestations of the disease.

The plasma lipoids in experimental atheroma.—The first and obvious factor in the animal experiments is hypercholesterolæmia. This, again with the exception of the experiments on choline deficiency, is present in all the animals which develop atheroma. It can be achieved in herbivorous animals merely by adding an excess of cholesterol to the diet; in other species, accustomed to the metabolism of some exogenous cholesterol, some supplementary procedure is necessary before sustained hypercholesterolæmia can be achieved by dietary means. Thus depression of thyroid function in dogs and, apparently, deficiency of sulphur-containing amino acids in monkeys, will bring about this result.

The level of cholesterolæmia attained in these experiments is usually greatly in excess of the normal range in man, and at first this appears to limit their significance in terms of human pathology. There is, however, an increasing amount of evidence that the severity of lesions in experimental animals cannot be related directly to absolute concentration of plasma cholesterol: that more important factors in pathogenesis appear to be the relative proportion of the different plasma lipoids and the type of association which the lipoids form with the

plasma proteins. This gives rise to the concept that the stability of the plasma cholesterol as a colloidal solution is more important than its absolute concentration.

It has been found for example that some procedures which augment the degree of hypercholesterolæmia which follows cholesterol feeding in rabbits may actually diminish the expected severity of the aortic lesions. This effect has been observed in rabbits with alloxan diabetes (Duff and McMillan, 1949; Duff and Payne, 1950), and following administration of cortisone (Adlersberg *et al.*, 1954) or the detergents Tween 80 and Triton A20 (Kellner *et al.*, 1951; Payne and Duff, 1951). Hypercholesterolæmia in these animals is accompanied by a greater increase in phospholipoid and neutral fat in the plasma than would occur with cholesterol feeding alone. Thus lesions form less readily, even in gross hyperlipæmia, when the relative proportions of the various plasma lipoids approximate more closely to the normal ratios.

To consider now the nature of the plasma lipoproteins in experimental animals: it appears from data quoted by Barr (1953) that the distribution of cholesterol between the α-lipoproteins and the larger β-lipoproteins in animals developing atheroma is similar to that occurring normally in man, and differs significantly from the distribution occurring in control animals. In both the rabbit and the dog with atheroma the greater proportion of the plasma cholesterol appears to be associated with the β-lipoproteins—a reversal of the situation occurring in the normal animal. The suggestion has therefore been put forward that the presence of a high concentration of cholesterol-containing β-lipoprotein in the blood is a significant factor in atherogenesis, and that, while this state occurs only in association with hypercholesterolæmia in experimental animals, it may occur within the normal range of cholesterol values in man (Barr *et al.*, 1953).

This concept of the importance of β-lipoproteins in atherogenesis has been carried a stage farther by Gofman and his group. Using the ultracentrifuge, they have separated a number of components in the β-lipoprotein complex according to differences in density. The only lipoprotein of this class in the normal rabbit contains approximately 30% cholesterol and moves in the ultracentrifuge at a rate, expressed in Svedberg units of flotation, as Sf 5-8. More rapidly moving components up to the visible chylomicra increase transitorily during the course of alimentary lipæmia. When the rabbit is fed cholesterol, there is at first an increase up to fourfold in the concentration of the normal component, followed by the appearance of a new class, designated Sf 10–30, and with more prolonged feeding, even more rapidly moving components, Sf 100 and above. These workers then go on to claim that there is a significant correlation between the concentration of this new class of lipoprotein (Sf 10–30) and the degree of atheroma in rabbits (Gofman *et al.*, 1950); this is the case not only when these animals are fed cholesterol alone, but also in alloxan diabetes and with cortisone treatment, where, as has been pointed out, there is no correlation between absolute cholesterol values and atheroma (Pierce, 1952; Pierce and Bloom, 1952). In such animals it is stated that most of the plasma cholesterol is associated with lipoproteins of the Sf 100 class and above, and that these classes are not atherogenic. The Sf 10–30 lipoproteins have also been identified in the blood of Cebus monkeys with atheroma (Mann *et al.*, 1953).

It appears from Gofman's work that the Sf 10–30 lipoproteins are not responsible for the visible lipæmia in cholesterol-fed rabbits and that this is due to different components of the β-lipoprotein complex consisting of larger visible lipoid particles which can be separated by centrifugation at relatively low speeds. In normal animals, ingested lipoid enters the blood from the thoracic duct, mostly in the form of visible particles—the chylomicra. It seems probable that this lipoid leaves the blood again only after the particles have been reduced to a more diffusible form; and there is increasing evidence that this process is related to the so-called heparin clearing reaction (Robinson *et al.*, 1954). In the cholesterol-fed rabbit, visible lipoid particles can be separated from the plasma by centrifugation, but some of these, unlike the chylomicra from the thoracic duct, have a very high cholesterol content and cannot be dispersed in the heparin clearing reaction (French *et al.*, 1955). This suggests that in the rabbit developing atheroma there are lipoid particles circulating in the blood which cannot be reduced to a diffusible form by the normal physiological process.

Deposition of lipoid in the intima of arteries.—There seems to be good evidence that in the cholesterol-fed rabbit there is an accumulation in the plasma of abnormal lipoprotein macromolecules and also abnormal larger lipoprotein aggregates of size comparable to the chylomicra in normal animals. The recognition of these abnormalities does not provide an adequate explanation of the lesions, however, unless it is known how the abnormal lipoid crosses the endothelial lining and comes to be deposited in the aortic intima.

The most widely held view is that it is due to a process of filtration (Page, 1954). According to this view the lipoid deposits are derived from lipoprotein molecules small enough to pass through the endothelium and yet sufficiently unstable to become deposited and engulfed by macrophages in the intimal connective tissue. An acceptance of this view appears to be implicit in Gofman's theory of atherogenesis. Thus, from a wide range of lipoprotein

aggregates in plasma, only those within a limited range satisfy criteria of diffusibility and instability which would be necessary to produce lesions. There is evidence, from a study of lymph in cholesterol-fed rabbits, that a proportion of the β-lipoprotein can circulate in the tissue fluid, and this seems to give some support to the filtration hypothesis (Kellner and Chang, 1950; Morris and Courtice, 1955).

On the other hand, several observations on the histological appearances in the early stages of the intimal lesions have suggested that the plasma lipoid is taken up by macrophages before it has passed through the endothelium. Macrophages laden with lipoid material have been described adhering first to the endothelial surface. They appear to be incorporated in the intima later, either migrating inwards (Leary, 1941), or being overgrown by proliferating endothelial cells (Rannie and Duguid, 1953). Unstable colloids, including cholesterol sols, when injected intravenously have been seen to deposit on the aortic intima and to provoke lesions very similar to atheroma (Hueper, 1942; Bevans *et al.*, 1948; Pollak and Wadler, 1951). Thus it seems possible that non-diffusible lipoproteins may be more important in causing intimal lesions than those which, like the Sf 10–30 class, are believed to pass directly through the endothelial lining of the vessel wall.

The further investigation of this problem of how lipoid enters the intima in experimental animals may well help to resolve the controversial question of whether atheroma begins under or over the endothelium.

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Professor H. W. Fullerton: *The Role of Diet in the Pathogenesis of Coronary Artery Disease*

Recent years have seen a marked increase in attempts to solve some of the problems of atheroma and coronary thrombosis, and, in reviewing the important researches which have occurred in this field, one is forced to the conclusion that, in the past, progress may have been delayed for long by the general acceptance of two theories; (1) the view of Virchow that the essential lesion in atheroma is a primary degeneration of the arterial wall, and (2) the conception that cholesterol *per se* plays a primary role in the production of atheromatous lesions. With regard to the first, Duguid (1949, 1952) has done much to renew interest in the earlier view of Rokitansky, and has presented convincingly the "thrombosis hypothesis" as the earliest phase in the development of atheroma. Acceptance of this hypothesis leads logically to a consideration of factors which may favour fibrin formation in the circulating blood. The second theory responsible for delay in progress, namely that cholesterol *per se* plays a dominant role in the production of atheromatous lesions, has resulted from several considerations: (1) the experimental work in rabbits, in which lesions similar to atheroma follow a high cholesterol intake (Anitschkow, 1933); (2) the established fact that atheromatous

lesions in humans often contain large amounts of cholesterol; and (3) the large volume of work which indicates that in atheroma in man, the serum cholesterol level is often greater than normal. However, the role of cholesterol is brought into clearer perspective when the following facts are kept in mind: (1) The amount of cholesterol needed to produce the atheromatous lesions in rabbits is extremely high as compared with the dietary intake of cholesterol in man. Moreover, although similar lesions have been produced in the chick, it needs high-cholesterol feeding plus thyroidectomy to duplicate this effect in the dog (Keys, 1952). Keys (1952) summarizes the significance of this work as follows: "From the animal experiments alone the most reasonable conclusion would be that the cholesterol content of human diets is unimportant in human atherosclerosis." (2) It must be borne in mind that atheromatous lesions often contain neutral fat and fatty acids as well as cholesterol. (3) It has been shown by Keys *et al.* (1950) and Hildreth *et al.* (1951) that the serum cholesterol is readily raised by increasing the dietary fat but it is not clearly related to the habitual intake of cholesterol. Accordingly, the large amount of evidence which points to a relationship between atheroma and high levels of serum cholesterol simply indicates that the dietary intake of fat is high in atheroma.

My main object is to consider briefly the evidence for an association between atheroma and a high dietary intake of fat, and, in doing so, I propose to accept the contention of Duguid that the formation of fibrin and its deposition on the arterial intima is a common and recurrent event in most of us and that these fibrin deposits form the essential starting point of atheroma.

It is generally accepted that coronary thrombosis, which is usually regarded as secondary to atheroma, has been increasing for many years in this country and that it affects the professional more than the labouring classes. It seems clear that there has been an increase in dietary fat since the early part of this century, and, in fact, this is the most notable dietary change which has occurred (Table I).

TABLE I.—ESTIMATED CONSUMPTION PER HEAD OF CERTAIN FOODS IN THE UNITED KINGDOM AT THREE PERIODS

A. Annual		1909–13	1924–28	1934	
	Butter	16 lb.	16 lb.	25 lb.	
	Eggs	104	120	152	
	Margarine	6 lb.	12 lb.	8 lb.	
B. Daily		1909–13	1924–28	1934	
	Fat	99	110	124	grams
	Protein	86	85	87	
	Carbohydrates	436	431	425	
	Calories	3,057	3,139	3,246	

Orr's findings in the inter-war years in different income groups are also of interest. He divided the population into groups according to the income per head per week; Group 1, up to 10s.; Group 2, 10s.–15s.; Group 3, 15s.–20s.; Group 4, 20s.–30s.; Group 5, 30s.–45s.; and Group 6, over 45s. Table II shows the daily consumption in the different income groups.

TABLE II

Group	1	2	3	4	5	6	
Fat	72	99	110	121	131	142	grams
Protein	63	76	84	89	94	98	
Carbohydrates	348	381	395	403	406	396	
Calories	2,317	2,768	2,962	3,119	3,249	3,326	

(The data in Tables I and II are taken from Davidson, L. S. P., and Anderson, I. A. (1947) Textbook of Dietetics. 2nd edit. London, pp. 3–6.)

It is obvious that the greatest difference between the low-income groups and the high-income groups is in the fat intake. Accordingly the figures so far show a striking parallelism between dietary fat, the increase in coronary thrombosis, and its higher incidence in the professional classes.

Two further points linking the incidence of coronary thrombosis and the dietary intake of fat are as follows:

(1) Keys (1953) has shown that there is a strong correlation between the mortality from degenerative heart disease and the percentage of the total calories derived from fat in different countries with widely varying dietary habits.

(2) During the war in Norway there was a marked decrease in the mortality from circulatory

diseases coincident with a reduction in dietary fat by about half (Malmros, 1949; Closs and Dedichen, 1949). The correlation found in this country was not so clear but the reduction in the fat intake was very much less; in fact the dietary fat during the war represented about 86% of the pre-war value (Leitner, 1954). Since 1947 in this country there has been a renewed increase in the consumption of fats, and to quote from the Ministry of Food's publication on "Domestic Food Consumption and Expenditure, 1950, Annual Report of the National Food Survey Committee, 1952": "Probably the most marked change in the diet in 1950 was an increase in the fat content by 7% compared with 1949 and the protein content by 1%, although the energy value remained almost unchanged. In other words, total energy needs appear to have been satisfied by an increase in the consumption of bacon, meat, eggs and milk, cheese and fats, and a decrease in that of bread and other cereals, potatoes and other vegetables, and sugar and preserves".

The evidence so far then points to a close correlation between fat intake and degenerative heart disease and coronary thrombosis, and I believe that this association may be due directly to the lipæmia which follows the ingestion of large amounts of fat. One consideration which suggests that it is the lipæmia which is responsible is the striking incidence of thrombosis or atheroma in conditions associated with lipæmia, for example, diabetes, pregnancy, acute hæmorrhage, leukæmia, ether anæsthesia, nephrosis, hypothyroidism and idiopathic hyperlipæmia.

Effect of lipæmia on blood coagulability.—I wish now to refer briefly to some of our experimental work on the effect of alimentary lipæmia on blood coagulability. Experiments were done using the clotting time of whole blood in silicone-coated tubes as the measure of coagulability.

Preliminary results in four normal individuals showed a marked shortening of the clotting time during the phase of lipæmia three hours after the ingestion of a meal containing 85 grams of fat (2 eggs, 2½ oz. bacon, 1 to 1½ oz. butter, bread, tea with milk and sugar) (Table III).

TABLE III.—CLOTTING TIMES IN MINUTES (IN DUPLICATE) FASTING AND AFTER HIGH FAT MEAL

Fasting	3 hours	Difference
25, 25	15, 15	10
30, 30	15, 20	13
30, 30	10, 15	18
25, 25	15, 20	8

An extension of these observations in eleven individuals showed significant shortening of the clotting times in nine, in all of whom macroscopic lipæmia was present. In Cases 10 and 11 where no reduction occurred, macroscopic lipæmia was absent (Table IV).

TABLE IV.—CLOTTING TIMES (IN MINUTES) AFTER HIGH FAT MEAL

Case	Fasting	3 hours	3½ hours	4 hours	Difference
1	25, 27	20, 20	20, 23	15, 20	9
2	25, 25	15, 15	15, 15	10, 10	15
3	20, 20	10, 15	10, 10	14, 10	10
4	20, 25	20, 20	20, 15	15, 20	5
5	20, 20	10, 13	10, 10	10, 15	10
6	20, 20	15, 18	15, 12	15, 12	7
7	20, 25	10, 10	15, 15	—	12
8	25, 20	15, 20	20, 20	5, 10	15
9	15, 20	15, 10	10, 15	15, 20	5
10	20, 20	20, 25	20, 20	25, 20	0
11	15, 15	15, 15	12, 10	10, 14	4

As a control, similar observations were made in 9 patients after the ordinary ward breakfast (fat content 12–30 grams) (Table V).

TABLE V.—CLOTTING TIMES (IN MINUTES) AFTER WARD BREAKFAST

Fasting	3 hours	3½ hours	4 hours	Difference
15, 15	15, 20	15, 15	15, 15	0
15, 15	15, 20	15, 15	15, 15	0
20, 20	23, 25	20, 20	25, 25	0
30, 33	25, 27	25, 27	25, 25	6
20, 20	20, 18	20, 20	20, 22	1
25, 25	22, 25	25, 20	25, 25	3
25, 25	25, 25	25, 25	25, 25	0
30, 27	25, 25	25, 25	25, 25	3
20, 20	10, 15	10, 10	10, 15	10

There was no significant reduction in clotting time except in Case 9: this was the only patient who showed macroscopic lipæmia after this meal.

It was concluded (1) that the coagulability of blood was considerably increased as a result of the lipæmia which follows a fat-rich meal and (2) that in most individuals lipæmia of a degree sufficient to produce this effect significantly occurs only when the intake of fat is high. I suggest, therefore, that one factor responsible for the intermittent fibrin formation which has been postulated by Duguid is the ingestion of meals rich in fat, and the evidence presented earlier shows that the dietary intake of fat has increased markedly during this century. It seems clear that, in most of us, the amount of fat ingested with a meal exceeds on numerous occasions the critical level at which an increase in coagulability occurs. No doubt there are considerable individual variations in the effects produced by a high fat intake; these variations may be constitutional and there may be a sex difference accounting for the greater incidence of atheroma and its complications in men than in women. Certainly there is evidence that lipæmia following fat ingestion is greater in elderly people (Necheles *et al.*, 1949) and in those who have coronary arterial disease (Morrison *et al.*, 1949). Also it should be borne in mind that variations in fibrinolytic activity may be important in determining the onset of atheromatous lesions. It may be that a careful study of fibrinolysis in coronary thrombosis would yield valuable information.

In conclusion, it has to be conceded that any hypothesis which is presented as an explanation of the pathogenesis of atheroma must account in a reasonable manner for the marked increase in the incidence of coronary thrombosis. I submit that the theory I have outlined, namely that the ingestion of large amounts of fat leads to intravascular fibrin formation and so to an increase in atheroma, is one which can account very well for the higher incidence of coronary thrombosis. The dynamics of the circulation in the coronary arteries differ from those in any other situation in that the blood flow is greatly and sharply reduced during the ejection phase of ventricular systole. "The flow in the left coronary artery is practically completely arrested since the force exerted upon the branches of the vessel by the heart muscle is greater than the aortic pressure. The force exerted by the right ventricle upon the coronary vessels is considerably less than that exerted by the left, and for this reason the flow into the vessels supplying the right heart is probably curtailed to a much less extent during ventricular ejection" (Best and Taylor, 1939). This cessation or reduction of blood flow could be expected to allow deposition of pre-formed fibrin on the intima of the coronary tree and this may be the starting point of the atheromatous process. Certainly the conception accords well with the anatomical distribution of the atheromatous lesions.

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Dr. J. N. Morris and Dr. R. A. Dale: *Epidemiology of Coronary Atherosclerosis*

Epidemiology deals with health and disease of populations and groups. It is the main research technique of Public Health and Preventive Medicine, and is thus understandably much concerned nowadays with coronary artery disease. Fig. 1 shows two indicators of the recent increase of ischæmic heart disease in middle-aged males. Such evidence (taken with evidence from other sources, for example the incidence of ruptured ventricle found at medico-legal necropsy), although no single piece is in itself convincing, adds up to the strong suggestion that the increase is a true one, and not merely the result of the ageing of the population, improvements in diagnosis, &c. This increase in ischæmic heart disease is a most important factor in the unsatisfactory trend of mortality in middle-aged males recently seen in most of the English-speaking world.

Ischæmic or "coronary" heart disease arises on a basis of coronary atherosclerosis ("coronary artery disease" is an inclusive term) and usually there is much and/or severe

atherosclerosis. But the relationship is not a simple one. Everyday experience indicates that only a minority even of those with marked atherosclerosis develop clinical heart disease—at any rate in middle age. Moreover, there is no evidence that coronary atherosclerosis has recently been increasing; indeed, it is an old disease that was certainly very common at the beginning of the century when ischæmic heart disease apparently was not (Morris, 1951).

We need to know much more about the prevalence of coronary atherosclerosis in the population, and its distribution among various sections. Suggestions have recently emerged that ischæmic heart disease is related to social class (Class I has almost twice the mortality of Class IV), to urbanization (middle-aged men in large towns have a higher death-rate than countrymen; farmers and agricultural workers have a particularly low mortality), to physical activity of work (London bus drivers seem to have twice the "sudden death" rate of the bus conductors; civil service clerks, &c., twice the "early" or ninety-day mortality of postmen), and to cigarette smoking (in the American study middle-aged men who smoked a packet a day or more had twice the coronary mortality of non-smokers) (Hammond and Horn, 1954; Morris *et al.*, 1953; Registrar General, 1954.) It is important to know whether such favourable and unfavourable experiences are related to the underlying atherosclerosis, its quantity, severity, or distribution; or whether other factors are mainly involved, e.g. the liability to major thrombosis—or differences possibly in the capacity to deal with such thrombosis. The causes of these various processes may be different and thus, ultimately, the opportunities for control and prevention.

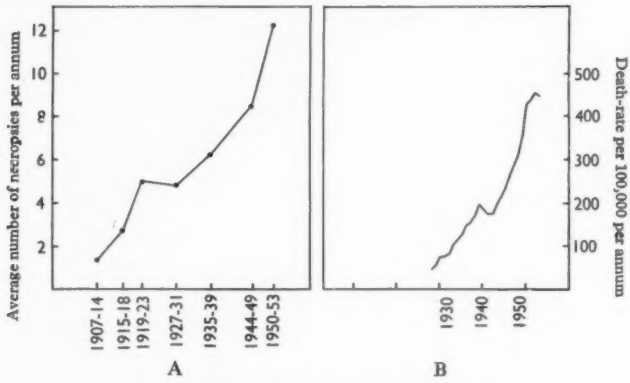

FIG. 1.—Increase of ischæmic heart disease.

A. London Hospital, males aged 35–69 years; average number of necropsies, recent coronary thrombosis, acute myocardial infarction, per year.

B. England and Wales, males aged 55–64 years; death-rates per 100,000, arteriosclerotic heart disease, per year.

We need to have, therefore, an analysis of coronary atherosclerosis as it occurs in the population. At the same time it would be interesting and useful to make a community study of the condition of the left ventricular myocardium (and septum) to see whether minor and subclinical ischæmic disease, as exemplified by the prevalence of scars, has a social distribution like that of the clinical disease described above. Such an epidemiological study is, however, exceedingly difficult since the only source is hospital post-mortem records. Now hospital *patients*, because of the selective factors, are incomplete sources of information about what is occurring in the general population. The use of hospital *necropsies* involves still further selection (e.g. the relatives' permission, and medical interest). It is out of the question to take "straight" hospital series and use them as indicators of prevalence in the population without some such adjustment as is described below.

Last year, we launched an enquiry asking all pathologists in Britain to send us reports on a consecutive series of 25 necropsies in middle-aged males, which the pathologists had carried out themselves, or for which they were responsible. The nation-wide approach was necessary to get big enough numbers and a big enough sample of occupations, a factor in which we are specially interested. There has been a very generous response. About two-thirds of the reports have so far come in and these are being analysed. Numbers are enough now to give us trends, but not for definitive statements on the social analyses.

TABLE I.—CORONARY ATHEROSCLEROSIS

CLASSIFICATION OF NECROPSIES BY MAIN CAUSE OF DEATH

GROUP A Deaths from Ischæmic Heart Disease	GROUP C—MISCELLANEOUS Deaths from Other Conditions
GROUP B Deaths from Conditions Associated with Coronary Atherosclerosis	GROUP D Mixed Unclassifiable

Table I shows a simple classification of necropsies by main cause of death in terms of coronary atherosclerosis. Necropsies can be classified in three main groups (the D group may be ignored for the present): deaths from ischæmic heart disease itself (A); deaths from such conditions as hypertension, deaths with diabetes, &c. (B); thirdly, there is the majority of deaths, Group C—deaths from cancer, injuries, infections, &c. If it is reasonable to make the assumption that *Group C* provides a picture of the great mass of the population, and of particular sections of it (that the group therefore in some measure represents the common *subclinical* coronary artery disease in general and in these sections), then this Group C can form the main element in a "model" of the coronary arteries and myocardium in the population. By feeding in correct proportions of deaths from ischæmic heart disease and deaths from hypertension, and so on, a model can be completed that will, at any rate, carry us a step farther towards a statistical account of the coronary arteries of the population.

Fig. 2 presents some of the results in Group C. The decreasing frequency, with age, of "No

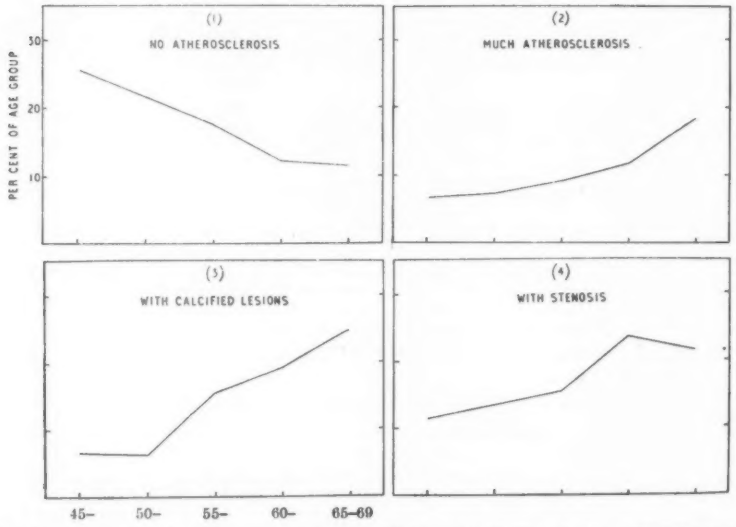

FIG. 2.—Group C, miscellaneous necropsies. Males aged 45–69 inclusive. Prevalence of coronary atherosclerosis in 2,201 cases.

Atherosclerosis" (1) as judged from naked-eye examination, and the increasing frequency with "Much Atherosclerosis" (2) are as expected. The irregular line "With calcified lesions" (3) is probably only "small-number trouble", though indeed the number of cases is relatively enormous (2,200 in this Group C alone and the smallest number of cases, at 45–49 is 219). The suggestion (4) of a decline in the frequency of noteworthy stenosis after a peak at 60–64 years is theoretically very interesting.

Again, working with these data the basic assumption made was that the miscellaneous Group C would give some idea of what is going on in the population as a whole. But the important question arises whether the condition of the coronary arteries is a contributory cause of the death of these men, whatever its main cause; and we are thus getting an exaggerated impression of the prevalence of coronary atherosclerosis. So far we have tested this proposition by making an analysis for necropsies from cancer of the bronchus, other

cancers and the rest of the miscellaneous Group C, the notion being that the condition of the coronary arteries is *unlikely* to be an important factor in mortality from cancer of the bronchus. Fig. 3 shows no difference that matters. (This finding incidentally is interesting

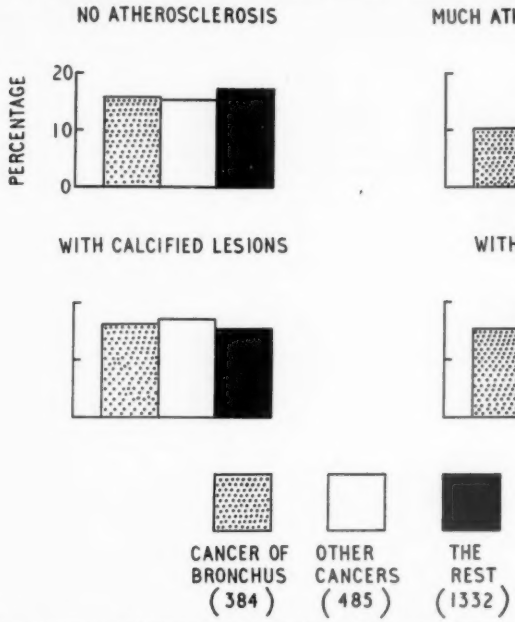

FIG. 3.—Group C, miscellaneous necropsies. Coronary atherosclerosis in three subgroups. Males aged 45–69 years.

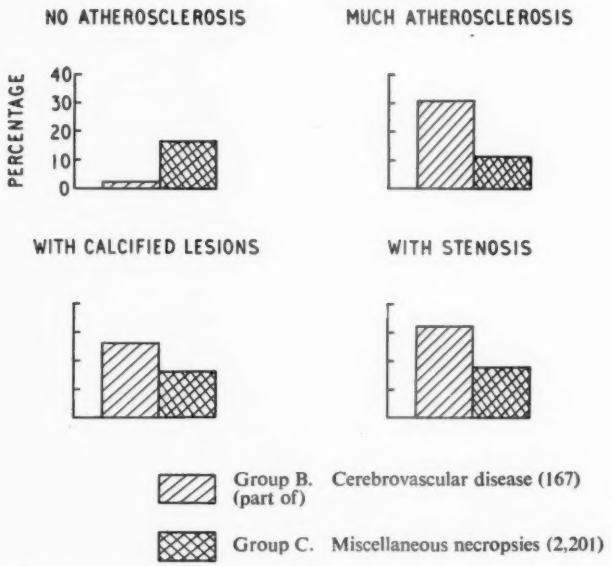

FIG. 4.—Prevalence of coronary atherosclerosis in a group with much hypertension and a group of miscellaneous necropsies. Males aged 45–69 years.

in relation to the work showing a connexion between smoking and coronary heart disease.)

Special groups.—A community model cannot be set up directly from hospital necropsies, because the proportions of deaths with hypertension, or with ischæmic heart disease itself, may vary considerably among these due to admission policies that have no reference to general trends of atherosclerosis in the population whence the necropsies derived. Fig. 4 shows the prevalence of coronary atherosclerosis in one "hypertensive" group compared with Group C. It is quite clear that these "hypertensives" have considerably more disease than the miscellaneous group. Fig. 5 makes the same point (with only one indicator)

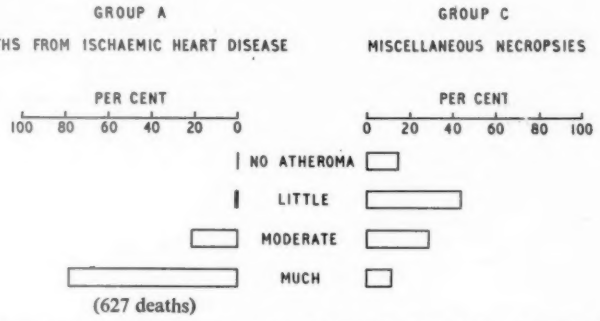

FIG. 5.—Prevalence of coronary atherosclerosis in deaths from ischæmic heart disease and a group of miscellaneous necropsies. Males aged 45–69 years.

for deaths from ischæmic heart disease, Group A: the picture of coronary atherosclerosis, in simple quantitative terms, is entirely different. There are, of course, no deaths with "No Atherosclerosis", very few with "Little", though quite a number with "Moderate" atheroma. The great majority of necropsies of ischæmic heart disease show "Much" atheroma. Again, therefore, the number of deaths from ischæmic heart disease included will obviously very much affect the total picture of atherosclerosis found in any hospital series. (However, it is worth noting that a fifth or a quarter of the deaths from ischæmic heart disease do not apparently have any very special amount of atherosclerosis.)

To set up the provisional model of coronary artery disease in the population to-day all the information available to us from morbidity and mortality studies on the prevalence of ischæmic heart disease, of hypertension and of diabetes in the population, has therefore also been used. Table II gives rough estimates for men in the late 40s and early 60s. We can,

TABLE II.—ESTIMATED PREVALENCE OF CORONARY ARTERY DISEASE

Ages ..	45–49	60–64
	Proportion of men: Approx.	
Much coronary atherosclerosis	10%	20%
Noteworthy stenosis in a main artery ..	13%	30%
Ischæmic scars in myocardium	3%	12%
Clinical ischæmic heart disease	1%	5%
Dying of ischæmic heart disease, p.a. ..	1 in 1,000	1 in 150

very provisionally, say that by the early sixties over 90% of males have some naked-eye coronary atherosclerosis: about 30% have a little, 40% have moderate amounts, and about 20%, as shown in Table II, much disease. Some 30% have noteworthy lumen narrowing in a main coronary artery. These figures may be regarded, at least, as showing order of magnitude. About 12% have ischæmic scars, and about 5% would appear from various morbidity studies to have clinical disease. Such figures as the last give an idea, however crude, of the epidemic proportions of the problem. The 5% is also interesting in relation to the 20 or 30% who have got material atherosclerosis. It emphasizes the point made earlier about many being susceptible—"eligible" in pathological terms—but relatively few apparently suffering. Clearly, it must not be assumed that coronary atherosclerosis and ischæmic heart disease are simple functions, one of the other.

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Dr. Z. A. Leitner:

I am gratified to notice that Professor Fullerton supports the concept of increased dietary fat intake in atherogenesis. In the past I have already referred in some detail to the increase of the fat calories as a percentage of total ingested calories in Western Europe and the U.S.A. in relation to the increased death-rate from coronary artery disease, and commented how far this tendency of increased fat intake may be connected with our present Western way of life (Leitner, 1954*a*, *b*).

This dietary theory of coronary heart disease does not pretend to be a null hypothesis, but it fits in well with all known facts, thus satisfying the requirements of a scientific theory. It is in accordance with the animal experiments that when blood cholesterol is sufficiently raised and maintained, atherosclerosis develops (Keys, 1953); that in groups of patients affected by coronary disease the blood cholesterol level is higher than in matched controls (Gertler and White, 1954); that high fat intake promotes lipæmia, which increases the coagulability of the blood and possibly promotes thrombus formation (Fullerton *et al.*, 1953); that emotional and physical stress raises the cholesterol level even on constant fat-poor diet (Groen *et al.*, 1952). This theory made it possible to predict low cholesterol levels in Naples and Madrid (Keys *et al.*, 1954) and very low cholesterol levels with very small incidence of atherosclerosis in the Bantu (Higginson and Pepler, 1954; Walker and Arvidson, 1954).

It is of comparatively little importance whether we refer to total blood cholesterol, to cholesterol/phospholipid ratio, to Sf fractions or to α- and β-lipoproteins, as they all are influenced by the diet. During the past five years, however, revolutionary developments have occurred in the study of blood lipids and some of the new knowledge reflects upon the possible causes of male preponderance in coronary heart disease. Although a great deal has still to be learned about the chemistry of lipoproteins, we know that about 60–70% of the serum cholesterol is contained in the β-lipoprotein fraction; the rest is carried by the α-lipoproteins. Whilst about 75% of the β-lipoprotein molecule consists of lipids and the rest of protein, the α-lipoprotein molecule contains only about 35% lipids and 65% proteins (Oncley *et al.*, 1950; Barr *et al.*, 1951). Incidentally œstrogens and carotenoids were found in the β-, and tocopherols in the α-lipoprotein fraction. It has been established (Barr, 1953) that the α-lipoproteins are present in larger amount in women and that this amount increases with age; in men their proportion is smaller and the amount does not increase with age. β-lipoproteins on the other hand are present in larger amounts in men and they increase with age in both sexes (Lewis and Page, 1953). (The α-lipoprotein fraction is excessive in newborn babies, in normal rabbits and dogs; in rabbits and dogs made atherosclerotic the α-lipoprotein diminishes by 80–90%.)

The preponderance of α-lipoproteins in women suggested an explanation for their comparative immunity from atherosclerosis and this knowledge led to the experimental use of œstrogens in men after coronary occlusion (Stamler *et al.*, 1954; Oliver and Boyd, 1954). The clinical application of this treatment is not yet practicable, but it can be stated with certainty that œstrogen administration is regularly followed by significant increase of the α-lipoproteins whilst androgens diminish this fraction; the β-lipoprotein fraction shows a reciprocal variation. Thus œstrogen administration in men suffering from coronary disease considerably depresses the β-lipoprotein fraction, the preponderance of which seems to be connected with severe atherosclerosis not only in men, but also as Dr. French pointed out, when experimental atherosclerosis had been produced in dogs. Incidentally, as Gofman's ultracentrifugal technique (Gofman *et al.*, 1954) does not include the separation of α-lipoproteins, his brilliant research has not been considered in this brief discussion. At the same time reference should be made to the interesting studies of the Harvard group (Gertler and White, 1954) on the prevalence of physical and mental masculinity in the "coronary individual".

Castration in the male and female is followed by an increase of the α-lipoprotein fraction (Furman, 1955). Coronary heart disease was indeed rarely observed in castrates in the past (White, 1952). In recent autopsy records of men treated with large doses of œstrogens on account of prostatic cancer less atherosclerosis was found than in the controls; in oophorec-

tomized (hypo-œstrogenic) women the incidence of severe atherosclerosis approached that of men; finally, in hyperœstrogenic women with breast cancer less atheromatosis was found than in the controls (Rivin and Dimitroff, 1954).

Thus it appears that sex hormones influence atherogenesis by some mechanism which includes the modification of the distribution of lipoproteins. This does not explain, however, why and how the metabolism of the arterial intima (particularly in the coronaries and aorta) has to undergo changes which lead to atheroma formation. Whether the outlined disturbance of fat metabolism is a fundamental defect, or only secondary to other causes, future histochemical research on the lines studied by Duguid (1954) and Crawford may clarify. But as it now appears that the freshly deposited atheromatous lesion is at least partly reversible in experimental animals, and is apparently halted or even reversed in castrates and by intensive hormonal treatment in men, we are justified in looking forward to some kind of prevention of this mortal disease of our Western civilization in the near future.

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Dr. J. E. Cotes, Mr. P. D. Oldham and Dr. Arthur J. Thomas: *The Prevalence of Coronary Heart Disease in a Mining Valley*

One of the difficulties in the study of coronary heart disease is to define the group to which the observations that one has made refer. This question arose in a study made by one of us (Thomas, 1955) into the prevalence of coronary heart disease amongst coal workers admitted to our ward with respiratory disease and who subsequently came to post-mortem. Was the observed prevalence representative of all the men in the appropriate age group, or did the findings only apply to the selected sample studied? To answer this question we studied a sample of men aged 55–64 selected at random from the whole population of miners in the Little Rhondda valley (Table I).

TABLE I

	Number
Population of Little Rhondda over age of 5 years	23,889
Total miners and ex-miners	6,513
Miners and ex-miners in 55–64 age group ..	1,160
Sample drawn	55
Dead or left district	4
Refusals	4
Men studied	47

The sample was drawn from the population defined as the result of a census conducted six months earlier (Cochrane, 1955). 55 men were selected, of whom 51 were living in the valley at the time of the present investigation and 47 (92%) submitted themselves to medical and physiological investigation.

The diagnosis of coronary heart disease was based on the clinical findings and on the

electrocardiograms. The diagnostic criteria included the lesser signs described by Evans and McRae (1952), which were found to be applicable in the presence of lung disease during the previous clinical and pathological study on the ward population.

Amongst the 47 subjects in the random sample, 18 were found to have coronary heart disease, giving a prevalence of 38%. 7 of these subjects (15% of the sample) had been in bed with the disease. The subjects had been selected at random irrespective of their clinical condition, and so it seemed legitimate to compare the blood pressure and body weight of those with and without coronary heart disease (Table II).

TABLE II

Coronary heart disease	Number of subjects	Mean body weight (lb.)	Mean blood pressure mm.Hg	
			Systolic	Diastolic
Yes	18	156·9 (range 120–220)	165·8 (range 112–250)	89·4 (range 50–125)
No	29	133·8 (range 102–173)	139·5 (range 110–210)	80·7 (range 65–110)

All apparent differences between the two groups are statistically significant at, at least, the 5% level.

We found, as has long been suspected, that the subjects who had coronary heart disease had a higher and more variable blood pressure, both systolic and diastolic, than the controls. The two groups also differed in their body weights, which were higher and more variable in the subjects with coronary heart disease. These cannot, of course, be regarded as independent findings since it is well known that blood pressure and body weight are positively correlated (Smirk, 1949).

A number of other comparisons were also made, and it is hoped to describe them more fully elsewhere. Our present purpose is to suggest that the technique of using a sample selected at random from the population appears to be a practical method of studying coronary heart disease.

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